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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *
* * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

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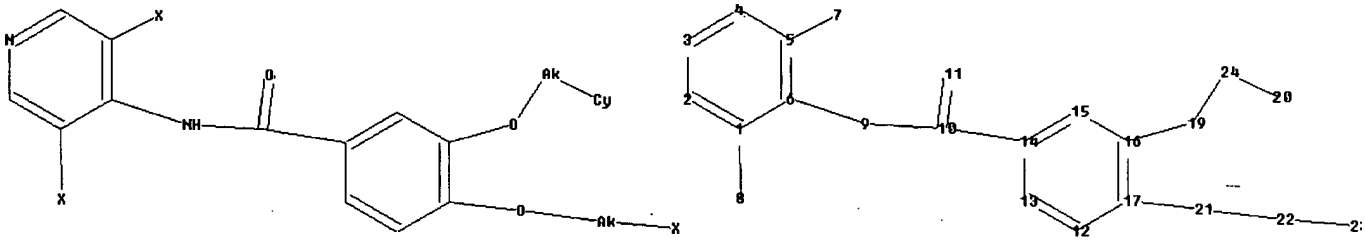

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ring nodes :
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chain bonds :
1-8  5-7  6-9  9-10  10-11  10-14  16-19  17-21  19-24  20-24  21-22  22-23
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  12-13  12-17  13-14  14-15  15-16  16-17
exact/norm bonds :
6-9  9-10  10-11  16-19  17-21  19-24  20-24  21-22  22-23
exact bonds :
1-8  5-7  10-14
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  12-13  12-17  13-14  14-15  15-16  16-17
isolated ring systems :
containing 1 : 12 :


Match level :
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11:CLASS  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:Atom  19:CLASS  20:Atom
21:CLASS  22:CLASS  23:CLASS  24:CLASS

=> s l1 sam
L2            2 SEA SSS SAM L1

=> s l1 full
L3           31 SEA SSS FUL L1

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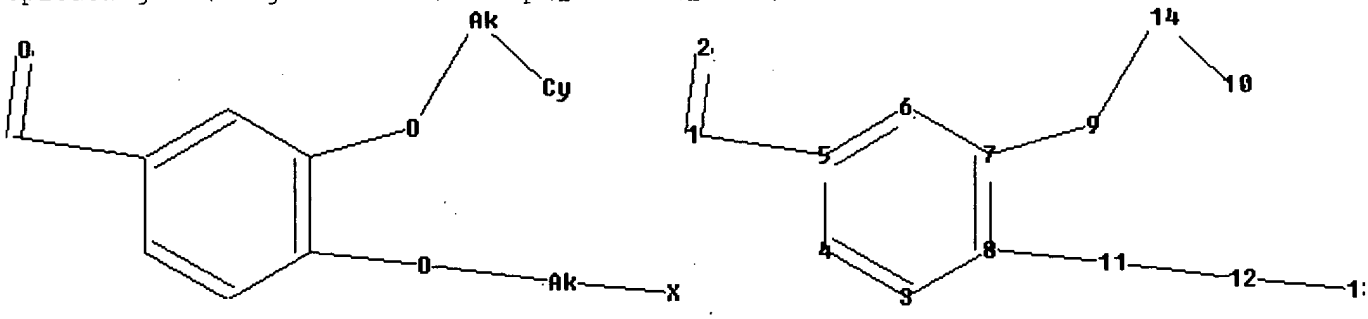

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1  2  9  10  11  12  13  14
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chain bonds :
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ring bonds :
3-4  3-8  4-5  5-6  6-7  7-8
exact/norm bonds :
1-2  7-9  8-11  9-14  10-14  11-12  12-13
exact bonds :
1-5
normalized bonds :
3-4  3-8  4-5  5-6  6-7  7-8


Match level :
1:CLASS  2:CLASS  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:CLASS  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:CLASS

=> s l4 sam
L5             2 SEA SSS SAM L4

=> s l4 full
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Intermediate Product

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L6            71 SEA SSS FULL L4


=> file caplus

=> s l3
L7          204 L3

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      23682210 PD< MARCH 2003
                 (PD<20030300)
L8           40 L7 AND PD< MARCH 2003

=> s l6
L9          221 L6

=> s l9 and pd< march 2003
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L10          49 L9 AND PD< MARCH 2003

=> s l8 and l10
L11          40 L8 AND L10

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L12           0 L8 NOT L11

=> s l11 not l8
L13           0 L11 NOT L8

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L8 ANSWER 1 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:586215 CAPLUS Full-text
DN 143:120526
TI Pharmaceutical compositions based on anticholinergics and additional active ingredients
IN Pairet, Michel; Pieper, Michael P.; Meade, Christopher John Montague; Reichl, Richard; Schmelzer, Christel; Jung, Birgit
PA Boehringer Ingelheim Pharma GmbH & Co. Kg, Germany
SO U.S. Pat. Appl. Publ., 50 pp., Cont.-in-part of U.S. Ser. No. 824,391. CODEN: USXXCO
DT Patent
LA English
FAN.CNT 14

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2005148562	A1	20050707	US 2004-6940	20041208	
	DE 10062712	A1	20020620	DE 2000-10062712	20001215	<--
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	US 2002151541	A1	20021017	US 2001-7182	20011019	<--
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	US 6620438	B2	20030916			
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	US 2003212075	A1	20031113	US 2003-419358	20030421	
	US 6696042	B2	20040224			
	US 2004024007	A1	20040205	US 2003-613783	20030703	
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	US 2004176338	A1	20040909	US 2004-776757	20040211	
	US 2004192675	A1	20040930	US 2004-824391	20040414	
	US 2005147564	A1	20050707	US 2005-68134	20050228	
PRAI	DE 2000-10054042	A	20001031			
	US 2000-253613P	P	20001128			
	DE 2000-10062712	A	20001215			
	DE 2000-10063957	A	20001220			
	US 2000-257220P	P	20001221			
	US 2000-257221P	P	20001221			
	DE 2001-10110772	A	20010307			
	DE 2001-10111058	A	20010308			
	DE 2001-10113366	A	20010320			
	US 2001-281653P	P	20010405			
	US 2001-281857P	P	20010405			
	US 2001-281874P	P	20010405			
	DE 2001-10138272	A	20010810			
	US 2001-314599P	P	20010824			
	US 2001-7182	B1	20011019			
	US 2001-86145	B1	20011019			

US 2001-27662	B1	20011220
DE 2002-10206505	A	20020216
US 2002-92116	A1	20020306
US 2002-93240	B1	20020307
US 2002-100659	A1	20020318
US 2002-369213P	P	20020401
US 2003-360064	A2	20030207
US 2003-413065	B2	20030414
US 2003-419358	A1	20030421
US 2003-613783	A2	20030703
US 2004-763894	A2	20040123
US 2004-775901	A2	20040210
US 2004-776757	A2	20040211
US 2004-824391	A2	20040414
US 2001-40196	B1	20011025
US 2003-395777	A1	20030324

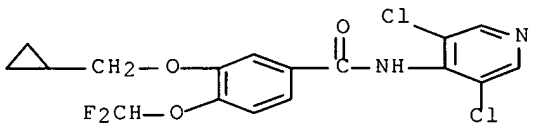
OS MARPAT 143:120526

AB A pharmaceutical composition comprising an anticholinergic and at least one addnl. active ingredient selected from among corticosteroids, dopamine agonists, PDE-IV inhibitors, NK1-antagonists, endothelin antagonists, antihistamines, and EGFR-kinase inhibitors, processes for preparing them and their use in the treatment of respiratory diseases. Among a number of compds. prepared was N-[2-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-[4-[(3-hydroxypropyl)methylamino]piperidin-1-yl]-N-methyl-2-phenylacetamide. Inhalable powders include a formulation containing tiotropium bromide, budesonide, and lactose.

IT 162401-32-3, Roflumilast
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. based on anticholinergics and addnl. active ingredients)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 2 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:37302 CAPLUS Full-text

DN 142:290459

TI Phosphodiesterase-4 (PDE4) as a target for anti-inflammatory drug discovery: Current status and future direction

AU Wang, Peng; Billah, M. Motasim

CS Allergy and Immunology Department, Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA

SO Recent Research Developments in Life Sciences (2003), 1(Pt. 2), 275-290
CODEN: RRDLCI

PB Research Signpost

DT Journal; General Review

LA English

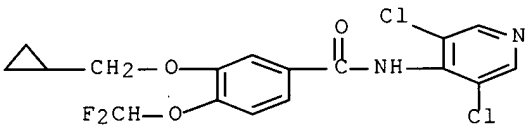
AB A review. Type 4 cAMP-specific phosphodiesterase (PDE4) is one of the most popular drug targets. PDE4 inhibitors have exhibited efficacy for several

inflammatory diseases including asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis and atopic dermatitis in the clinic, and for several other conditions such as arthritis and sepsis in animal models. Clin. development of first generation PDE4 inhibitors (such as rolipram and piclamilast) has been discontinued due to emetic side-effect. Several second generation PDE4 inhibitors (such as cilomilast and roflumilast) are currently under development. However, they are still not devoid of the emetic side-effect, and hence their clin. doses are limited. PDE4 family comprises four subtypes. Current PDE4 inhibitors in general do not distinguish between various subtypes. Recently, there has been significant progress in the understanding of differential roles of various PDE4 subtypes. Inhibitors for specific PDE4 subtype(s) may have reduced side-effect potential while maintaining the anti-inflammatory activity, and hence provide significant improvement over current PDE4 inhibitors.

IT 162401-32-3, Roflumilast
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific phosphodiesterase-4 subtype B2 inhibitor significantly improve anti-inflammatory activity by reducing emetic side effect than phosphodiesterase-4 inhibitor roflumilast)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 157 THERE ARE 157 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2004:9403 CAPLUS Full-text

DN 140:399072

TI Phosphodiesterase-4 inhibitors in the treatment of inflammatory lung disease

AU Spina, Domenico

CS The Sackler Institute of Pulmonary Pharmacology, GKT School of Biomedical Science, King's College London, London, UK

SO Drugs (2003), 63(23), 2575-2594
CODEN: DRUGAY; ISSN: 0012-6667

PB Adis International Ltd.

DT Journal; General Review

LA English

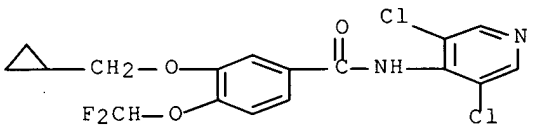
AB A review. Phosphodiesterases (PDE) belong to an important family of proteins that regulate the intracellular levels of cyclic nucleotide second messengers. Targeting PDE with selective inhibitors may offer novel therapeutic strategies in the treatment of various conditions, and in the context of respiratory disease these include asthma and chronic obstructive pulmonary disease (COPD). The rationale for such an approach stems, in part, from the clin. efficacy of theophylline, an orally active drug that is purportedly a nonselective PDE inhibitor. In addition, intracellular cyclic adenosine monophosphate (cAMP) levels regulate the function of many of the cells thought to contribute to the pathogenesis of respiratory diseases such as asthma and COPD, and these cells also selectively express PDE4. This has offered pharmaceutical companies the opportunity to selectively target these enzymes for the treatment of these

diseases. Finally, the success of targeting PDE5 in the treatment of erectile dysfunction provides clin. proof of concept for the targeting of PDE in disease. Whether a Viagra of the airways can be found for the treatment of asthma and COPD remains to be seen, but pos. results from recent clin. studies examining the efficacy of selective PDE4 inhibitors such as cilomilast and roflumilast offer some optimism. However, one of the major issues to be resolved is the tolerability profile associated with this drug class that is a consequence of PDE4 inhibition. While cilomilast and roflumilast have low emetic potential they are not free from emesis and various strategies are being investigated in the hope of developing a PDE4 inhibitor without this adverse effect.

IT 162401-32-3, Roflumilast
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase-4 inhibitors in the treatment of inflammatory lung disease)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 177 THERE ARE 177 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:775801 CAPLUS Full-text

DN 140:104939

TI Inhibition of inflammation and remodeling by roflumilast and dexamethasone in murine chronic asthma

AU Kumar, Rakesh K.; Herbert, Cristan; Thomas, Paul S.; Wollin, Lutz; Beume, Rolf; Yang, Ming; Webb, Dianne C.; Foster, Paul S.

CS Department of Pathology, University of New South Wales, Sydney, Australia

SO Journal of Pharmacology and Experimental Therapeutics (2003), 307(1), 349-355
CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics

DT Journal

LA English

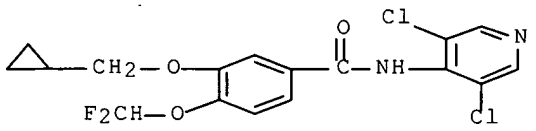
AB Phosphodiesterase (PDE) inhibitors have potential as alternatives or adjuncts to glucocorticoid therapy in asthma. We compared roflumilast (a selective PDE4 inhibitor) with pentoxifylline (a nonselective inhibitor) and dexamethasone in ameliorating the lesions of chronic asthma in a mouse model. BALB/c mice sensitized to ovalbumin were chronically challenged with aerosolized antigen for 6 wk. During weeks 5 and 6, groups of animals were treated with roflumilast or dexamethasone by daily gavage or with pentoxifylline by daily i.p. injection. Airway hyper-reactivity (AHR) was evaluated by wholebody plethysmog. and airway lesions by histomorphometry and immunohistochem. Compared with vehicle alone, treatment with roflumilast or dexamethasone significantly reduced accumulation of eosinophils and chronic inflammatory cells, subepithelial collagenization, and thickening of the airway epithelium. Dexamethasone also reduced goblet cell hyperplasia/metaplasia, subepithelial accumulation of transforming growth

factor-β1, and epithelial cytoplasmic immunoreactivity for nuclear factor-κB. Treatment with pentoxifylline inhibited only eosinophil recruitment and epithelial thickening. Roflumilast and dexamethasone slightly decreased AHR, whereas this was significantly reduced by pentoxifylline. Thus, in this model of chronic asthma, both roflumilast and dexamethasone were potent inhibitors of airway inflammation and remodeling. Roflumilast did not diminish accumulation of transforming growth factor-β1, suggesting that it might affect remodeling by mechanisms distinct from glucocorticoids.

IT 162401-32-3, Roflumilast
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of inflammation and remodeling by roflumilast and dexamethasone in murine chronic asthma)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:749998 CAPLUS Full-text
DN 139:255370
TI Synergistic combination
IN Kilian, Ulrich; Schudt, Christian
PA Altana Pharma A.-G., Germany
SO U.S., 29 pp., Cont.-in-part of U. S. Ser. No. 367,850.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6624181	B1	20030923	US 2002-49999	20020220
	WO 9837894	A1	19980903	WO 1998-EP1047	19980224 <--
	W: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6333354	B1	20011225	US 1999-367850	19990827 <--
	WO 2001013953	A2	20010301	WO 2000-EP7852	20000811 <--
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	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1671651	A1	20060621	EP 2006-110822	20000811
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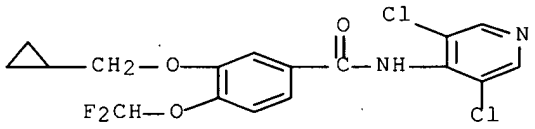
	US 2004034087	A1	20040219	US 2003-437005	20030514

	US 7056936	B2	20060606		
	US 2006079539	A1	20060413	US 2005-286391	20051125
	US 2006205806	A1	20060914	US 2006-433419	20060515
PRAI	DE 1997-19708049	A	19970228		
	WO 1998-EP1047	W	19980224		
	EP 1999-116447	A	19990821		
	US 1999-367850	A2	19990827		
	WO 2000-EP7852	W	20000811		
	EP 2000-954625	A3	20000811		
	US 2002-49999	A1	20020220		
	US 2003-437005	A1	20030514		
	US 2005-286391	A1	20051125		

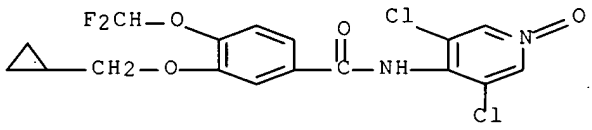
AB The invention relates to the combined administration of PDE inhibitors, such as roflumilast, and β2 adrenoceptor agonists for the treatment of respiratory tract disorders.

IT 162401-32-3, Roflumilast 292135-78-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic combination of PDE inhibitors and β2-adrenoceptor agonists for therapy of respiratory tract disorders)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 292135-78-5 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

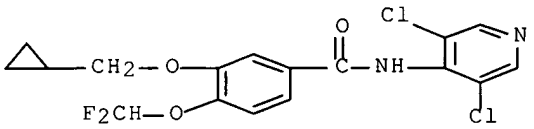
L8 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:157374 CAPLUS Full-text
DN 139:239375
TI Roflumilast Altana Pharma
AU Reid, Peter
CS Western General Hospital, Edinburgh, EH4 2XU, UK
SO Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2002), 3(8), 1165-1170
CODEN: COIDAZ; ISSN: 1472-4472
PB PharmaPress Ltd.
DT Journal; General Review
LA English

AB A review. Roflumilast is a specific PDE4 inhibitor being developed by Altana Pharma (formerly known as Byk Gulden) for the potential treatment of asthma and chronic obstructive pulmonary disease.

IT 162401-32-3P, Roflumilast
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibitor; roflumilast bronchodilator antiinflammatory asthma obstructive lung disease)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2003:5806 CAPLUS Full-text

DN 138:78456

TI Composition comprising a PDE-4 inhibitor and H1-receptor antagonist for treatment of respiratory diseases

IN Knowles, Richard Graham; Ward, Peter; Nials, Anthony Terence

PA Glaxo Group Limited, UK

SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003000289	A1	20030103	WO 2002-GB2679	20020617 <--
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	AU 2002310620	A1	20030108	AU 2002-310620	20020617 <--
	EP 1404369	A1	20040407	EP 2002-735611	20020617
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	HU 2004000222	A2	20040728	HU 2004-222	20020617
	CN 1518460	A	20040804	CN 2002-812473	20020617
	BR 2002010473	A	20040810	BR 2002-10473	20020617
	JP 2005501023	T	20050113	JP 2003-506932	20020617
	US 2004176419	A1	20040909	US 2003-480969	20031208
	IN 2003DN02141	A	20060120	IN 2003-DN2141	20031209

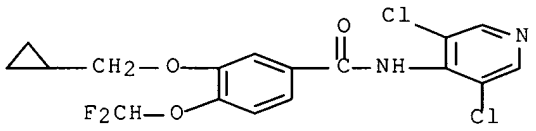
	ZA 2003009587	A	20050117	ZA 2003-9587	20031210
	MX 2003PA11702	A	20040319	MX 2003-PA11702	20031216
PRAI	GB 2001-15181	A	20010620		
	WO 2002-GB2679	W	20020617		

AB A method of prophylaxis, treating, or reducing the duration or frequency of the exacerbations associated with a respiratory disease, such as chronic obstructive pulmonary disease or asthma, comprises administering to a patient an effective amount of a phosphodiesterase-4 (PDE-4) inhibitor, e.g., cilomilastat, in combination with an H1-receptor antagonist, e.g., loratadine. For example, a metered dose inhaler (e.g., for 120 actuations) was prepared containing cilomilast 18 mg, loratadine 12 mg, and 1,1,1,2-tetrafluoroethane to 75.0 mg.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising PDE-4 inhibitor and H1-receptor antagonist for treatment of respiratory diseases)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:965129 CAPLUS Full-text
DN 138:44711
TI Pharmaceutical compositions based on anticholinergics and PDE-IV inhibitors
IN Pairet, Michel; Meade, Christopher J. M.; Pieper, Michael P.
PA Germany
SO U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Provisional Ser. No. 281,857.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 14

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002193393	A1	20021219	US 2002-93240	20020307 <--
	DE 10110772	A1	20020912	DE 2001-10110772	20010307 <--
	US 2004024007	A1	20040205	US 2003-613783	20030703
	US 2005148562	A1	20050707	US 2004-6940	20041208
PRAI	DE 2001-10110772	A	20010307		
	US 2001-281857P	P	20010405		
	DE 2000-10054042	A	20001031		
	US 2000-253613P	P	20001128		
	DE 2000-10062712	A	20001215		
	DE 2000-10063957	A	20001220		
	US 2000-257220P	P	20001221		
	US 2000-257221P	P	20001221		
	DE 2001-10111058	A	20010308		
	DE 2001-10113366	A	20010320		

	US 2001-281653P	P	20010405
	US 2001-281874P	P	20010405
	DE 2001-10138272	A	20010810
	US 2001-314599P	P	20010824
	US 2001-7182	B1	20011019
	US 2001-86145	B1	20011019
	US 2001-27662	B1	20011220
	DE 2002-10206505	A	20020216
	US 2002-92116	A1	20020306
	US 2002-93240	B1	20020307
	US 2002-100659	A1	20020318
	US 2002-369213P	P	20020401
	US 2003-360064	A2	20030207
	US 2003-413065	B2	20030414
	US 2003-419358	A1	20030421
	US 2003-613783	A2	20030703
	US 2004-763894	A2	20040123
	US 2004-775901	A2	20040210
	US 2004-776757	A2	20040211
	US 2004-824391	A2	20040414

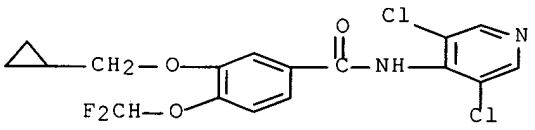
OS MARPAT 138:44711

AB The present invention relates to novel pharmaceutical compns. based on anticholinergics and phosphodiesterase (PDE) IV inhibitors, processes for preparing them and their use in the treatment of respiratory tract diseases. For example, a suspension aerosol contained tiotropium bromide 0.029%, AWD 12-281 0.033%, ethanol 0.5%, iso-Pr myristate 0.1%, and TG 227 to 100%.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalation compns. based on anticholinergics and phosphodiesterase IV inhibitors for treatment of respiratory tract diseases)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:849588 CAPLUS Full-text

DN 137:353054

TI Preparation of pyrimidinylaminothiazolecarboxylates and related pyrimidines as dual inhibitors of phosphodiesterases PDE 7 and PDE 4

IN Pitts, William John; Watson, Andrew J.; Dodd, John H.

PA Bristol-Myers Squibb Company, USA

SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002088080	A2	20021107	WO 2002-US13742	20020430 <--
	WO 2002088080	A3	20030313		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2444436	A1	20021107	CA 2002-2444436	20020430 <--
AU 2002256419	A1	20021111	AU 2002-256419	20020430 <--
US 2003104974	A1	20030605	US 2002-135998	20020430
EP 1383743	A2	20040128	EP 2002-725882	20020430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 2004000718	A2	20040728	HU 2004-718	20020430
JP 2004532233	T	20041021	JP 2002-585382	20020430
US 2006116516	A1	20060601	US 2005-281246	20051117
PRAI US 2001-287964P	P	20010501		
US 2001-299287P	P	20010619		
US 2002-368752P	P	20020329		
WO 2002-US13742	W	20020430		
US 2002-173322	A3	20020617		

OS MARPAT 137:353054

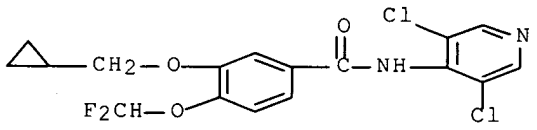
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Dual inhibitors of PDE 7 and PDE 4 (pyrimidines, e.g. I), together with their use to treat leukocyte activation-associated disorders (including transplant rejection, rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma, chronic obstructive pulmonary disease, lupus and multiple sclerosis), are provided herein. The present invention further provides for a method of reducing or alleviating nausea and emesis associated with the administration of PDE4 inhibitors comprising either the administration of a dual PDE 7-PDE 4 inhibitor, or the simultaneous or sequential co-administration of a selective PDE 7 inhibitor together with a selective PDE 4 inhibitor. In I, R1a is H or alkyl; R2a is optionally substituted heteroaryl; Z is halogen, alkyl, substituted alkyl, haloalkyl, or NR3aR4a; R3a is H or alkyl; R4a is alkyl, optionally substituted (heteroaryl)alkyl, optionally substituted heterocyclo, optionally substituted (heterocyclo)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T1* and T2* and optionally further substituted with a group T3*; or R3a and R4a together with the N atom to which they are attached may combine to form an optionally substituted heterocyclo ring; R5a is (aryl)alkyl wherein the aryl group is substituted with one or two groups T1* and T2* and optionally further substituted with a group T3*; R6a is H or alkyl; R7a is H or alkyl; T1* and T2* are independently alkoxy, alkoxycarbonyl, heteroaryl or -SO2R8a where R8a is alkyl, amino, alkylamino or dialkylamino; or T1* and T2* together with the atoms to which they are attached may combine to form a ring (e.g., benzodioxole); T3* is H, alkyl, halo, haloalkyl or cyano. Other pyrimidine classes (II-V) are described in the claims; this patent differs from WO 02/088079 with regard to IV (J1 and J2 are same or different and are optionally substituted alkylene group of 1-3 C atoms, provided that they are not both greater than C2 alkylene). Pharmaceutical properties for 2-[[4-[4-(dimethylamino)-1-piperidinyl]-6-[[(3,4,5- trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid Et ester (F1) and 2-[4,6-bis(4-hydroxypiperidin-1-yl)pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid Et ester (F2) are

reported. F1 is 100 fold selective for PDE 7 over PDE 4 and F2 is >50 fold selective for PDE 7. The IC50 for lipolysaccharide peripheral blood mononuclear cells tumor necrosis factors (LPS PBMC TNF) was >25 μM for F2 while cilomilast was potent in this assay with an IC50 of 0.43 μM. Mice were administered 30 mg/kg IP of F1 and 45 min later were administered 10 mg of rolipram orally; the Cmax for F1 are essentially unchanged by co-administration of rolipram, and the Cmax of rolipram was reduced by a factor of 3 by co-administration with F1. Also, the plasma concentration of F1 when administered at 30 mg/kg does not reach the PDE 4 IC50 of F1. Compared to LPS-injected mice pretreated with vehicle, mice receiving F1 or rolipram alone had 52% and 54% redns. in serum TNF, resp. (each $p<.05$ vs. vehicle), as measured by a specific immunoassay, whereas mice treated with the combination of rolipram plus F1 showed an 89% reduction in serum TNF, which was significantly ($p<.05$) less than mice receiving either compound alone. Mice treated with dexamethasone showed a 93% reduction in serum TNF. Compound F2 inhibited TNF production by 33.7% which was not statistically significant, whereas cilomilast inhibited TNF production by 56% ($p < 0.05$); the combination group which received both cilomilast 1 mg/kg and compound F2, had a decrease in TNF production of 72% ($p < 0.05$ vs. cilomilast alone). Although the methods of preparation are not claimed, 27 example prepns. are included.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PDE 4 inhibitor; combined with pyrimidine PDE 7 inhibitors for reducing emesis or nausea associated with administration of PDE 4 inhibitor for treatment of leukocyte activation-associated diseases)
RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:849587 CAPLUS Full-text
DN 137:353053
TI Preparation of pyrimidinylaminothiazolecarboxylates and related pyrimidines as dual inhibitors of phosphodiesterases PDE 7 and PDE 4
IN Pitts, William John; Watson, Andrew J.; Dodd, John H.
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002088079	A2	20021107	WO 2002-US13628	20020429 <--
	WO 2002088079	A3	20030130		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	AU 2002305290	A1	20021111	AU 2002-305290	20020429 <--
	US 2003104974	A1	20030605	US 2002-135998	20020430
	US 2006116516	A1	20060601	US 2005-281246	20051117
PRAI	US 2001-287964P	P	20010501		
	US 2001-299287P	P	20010619		
	US 2002-368752P	P	20020329		
	WO 2002-US13628	W	20020429		
	US 2002-173322	A3	20020617		

OS MARPAT 137:353053
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

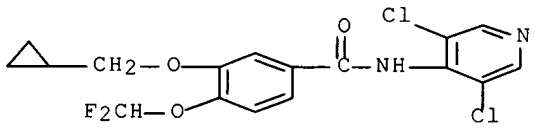
AB Dual inhibitors of PDE7 and PDE4, together with their use to treat leukocyte activation-associated disorders (including transplant rejection, rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma, chronic obstructive pulmonary disease, lupus and multiple sclerosis), are provided herein. Dual inhibitors of PDE 7 and PDE 4 (pyrimidines, e.g. I), together with their use to treat leukocyte activation-associated disorders (including transplant rejection, rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma, chronic obstructive pulmonary disease, lupus and multiple sclerosis), are provided herein. The present invention further provides for a method of reducing or alleviating nausea and emesis associated with the administration of PDE4 inhibitors comprising either the administration of a dual PDE 7-PDE 4 inhibitor, or the simultaneous or sequential co-administration of a selective PDE 7 inhibitor together with a selective PDE 4 inhibitor. In I, R1a is H or alkyl; R2a is optionally substituted heteroaryl; Z is halogen, alkyl, substituted alkyl, haloalkyl, or NR3aR4a; R3a is H or alkyl; R4a is alkyl, optionally substituted (heteroaryl)alkyl, optionally substituted heterocyclo, optionally substituted (heterocyclo)alkyl, or (aryl)alkyl wherein the aryl group is substituted with one or two groups T1* and T2* and optionally further substituted with a group T3*; or R3a and R4a together with the N atom to which they are attached may combine to form an optionally substituted heterocyclo ring; R5a is (aryl)alkyl wherein the aryl group is substituted with one or two groups T1* and T2* and optionally further substituted with a group T3*; R6a is H or alkyl; R7a is H or alkyl; T1* and T2* are independently alkoxy, alkoxycarbonyl, heteroaryl or -SO2R8a where R8a is alkyl, amino, alkylamino or dialkylamino; or T1* and T2* together with the atoms to which they are attached may combine to form a ring (e.g., benzodioxole); T3* is H, alkyl, halo, haloalkyl or cyano. Other pyrimidine classes (II-V) are described in the claims; this patent differs om WO 02/088080 with regard to IV (J1 and J2 are same or different and are a bond or optionally substituted alkylene group of 1-4 C atoms, provided that they are not both a bond, and further that if one is a bond the other is an alkylene group of at least 3 C atoms). Pharmaceutical properties for 2-[[4-[4-(dimethylamino)-1- piperidinyl]-6-[[(3,4,5-trimethoxyphenyl)methyl]amino]-2- pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid Et ester (F1) and 2-[4,6-bis(4-hydroxypiperidin-1-yl)pyrimidin-2-ylamino]-4-methylthiazole-5- carboxylic acid Et ester (F2) are reported. F1 is 100 fold selective for PDE 7 over PDE 4 and F2 is >50 fold selective for PDE 7. The IC50 for lipolysaccharide peripheral blood mononuclear cells tumor necrosis factors (LPS PBMC TNF) was >25 μM for F2 while cilomilast was potent in this assay with an IC50 of 0.43 μM. Mice were administered 30 mg/kg IP of F1 and 45 min later were administered 10 mg of

rolipram orally; the Cmax for F1 are essentially unchanged by co-administration of rolipram, and the Cmax of rolipram was reduced by a factor of 3 by co-administration with F1. Also, the plasma concentration of F1 when administered at 30 mg/kg does not reach the PDE 4 IC50 of F1. Compared to LPS-injected mice pretreated with vehicle, mice receiving F1 or rolipram alone had 52% and 54% redns. in serum TNF, resp. (each $p<.05$ vs. vehicle), as measured by a specific immunoassay, whereas mice treated with the combination of rolipram plus F1 showed an 89% reduction in serum TNF, which was significantly ($p<.05$) less than mice receiving either compound alone. Mice treated with dexamethasone showed a 93% reduction in serum TNF. Compound F2 inhibited TNF production by 33.7% which was not statistically significant, whereas cilomilast inhibited TNF production by 56% ($p < 0.05$); the combination group which received both cilomilast 1 mg/kg and compound F2, had a decrease in TNF production of 72% ($p < 0.05$ vs. cilomilast alone). Although the methods of preparation are not claimed, 27 example prepns. are included.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PDE 4 inhibitor; combined with pyrimidine PDE 7 inhibitors for reducing emesis or nausea associated with administration of PDE 4 inhibitor for treatment of leukocyte activation-associated diseases)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:697809 CAPLUS Full-text

DN 138:248180

TI Benefit of phosphodiesterase 4 inhibitors as supplemental therapy after lung transplantation concerning their antiproliferative effects: an experimental study using a heterotopic rodent model

AU Schade, Ina; Roth-Eichhorn, Sylke; Kasper, Michael; Kuss, Hildegard; Ploetze, Katrin; Funk, Richard H. W.; Schueler, Stephan

CS Cardiovascular Institute, University of Dresden, Dresden, Germany

SO Transplantation (2002), 74(3), 326-334
CODEN: TRPLAU; ISSN: 0041-1337

PB Lippincott Williams & Wilkins

DT Journal

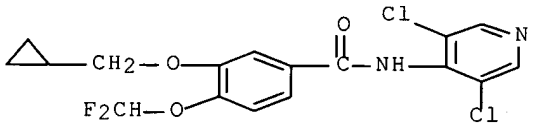
LA English

AB Background. Recent advances in the understanding of immunomodulatory properties of phosphodiesterase 4 (PDE4) inhibitors recommend these drugs for immunosuppressive therapy after lung transplantation. The potency of three PDE4 inhibitors was tested using an established model of heterotopic tracheal transplantation in rats. Methods. Five allogenic groups were investigated and treated with the PDE4 inhibitors: rolipram, cilomilast (Ariflo, SB-207499), roflumilast or cyclosporine A (CsA), or left without immunosuppression. The grafts were quant. analyzed for epithelial integrity, monocyte/macrophage content, cell proliferation, and tracheal obliteration by histol./immunohistochem. (days 1, 5, 7, 21, 28; n=4-7). Results. In animals treated with the PDE4 inhibitors, the epithelium was completely lost until day 21. The epithelium was partially preserved in the rats receiving CsA until day 28. In the acute phase (days 5 and 7) the infiltration of monocytes and

macrophages was significantly inhibited similarly (cilomilast) or less effective (rolipram, roflumilast) as in CsA-treated rats. In the chronic phase (day 28) the significant increase of monocytes and macrophages after CsA-treatment was not found in PDE4 inhibitor-treated rats. The PDE4 inhibitors showed lower (rolipram) or higher (cilomilast, roflumilast) potency as CsA to inhibit the cell proliferation. Only treatment with PDE4 inhibitor (Ariflo) significantly inhibited the obliteration, but to a lesser degree as CsA. Conclusion. The PDE4 inhibitors tested in our study are not suitable on their own for immunosuppressive therapy after lung transplantation because of the limited protection against the epithelial disturbance, infiltration of immune cells, and luminal obliteration. The strong anti-proliferative effect of the second-generation PDE4 inhibitors, cilomilast and roflumilast, suggest a benefit for the effective inhibition of immune cell and fibroblast proliferation contributing to the development of obliterative bronchiolitis.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benefit of phosphodiesterase 4 inhibitors as supplemental therapy after lung transplantation concerning their antiproliferative effects: an exptl. study using a heterotopic rodent model)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:695761 CAPLUS Full-text
DN 137:237718
TI Inhalant compositions containing anticholinergics and PDE IV inhibitors
IN Meade, Christopher John Montague; Pairet, Michel; Pieper, Michael Paul
PA Boehringer Ingelheim Pharma K.-G., Germany
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 14

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002069945	A2	20020912	WO 2002-EP1988	20020226 <--
	WO 2002069945	A3	20030130		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10110772	A1	20020912	DE 2001-10110772	20010307 <--

	CA 2439763	A1	20020912	CA 2002-2439763	20020226 <--
	AU 2002257587	A1	20020919	AU 2002-257587	20020226 <--
	AU 2002257587	B2	20070510		
	EP 1372649	A2	20040102	EP 2002-727329	20020226
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004521134	T	20040715	JP 2002-569122	20020226
	BR 2002007883	A	20040727	BR 2002-7883	20020226
	HU 2004000782	A2	20040728	HU 2004-782	20020226
	NZ 528621	A	20050429	NZ 2002-528621	20020226
	CN 1649588	A	20050803	CN 2002-805346	20020226
	ZA 2003006221	A	20040722	ZA 2003-6221	20030812
	IN 2003DN01295	A	20050527	IN 2003-DN1295	20030814
	MX 2003PA08045	A	20031204	MX 2003-PA8045	20030905
PRAI	DE 2001-10110772	A	20010307		
	WO 2002-EP1988	W	20020226		

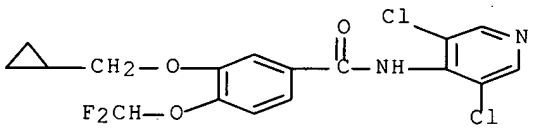
OS MARPAT 137:237718

AB The invention relates to drug compns. based on anticholinergics and PDE IV inhibitors, to methods for their production, and to their use as inhalants for the treatment of respiratory tract diseases. Thus an inhalation powder was composed of capsules that contained (μg/capsule): tiotropium bromide 21.7; AWD-12-281 200; lactose 4778.3.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalant compns. containing anticholinergics and PDE IV inhibitors)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 13 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:695727 CAPLUS Full-text

DN 137:226646

TI Co-administration of melanocortin receptor agonist and phosphodiesterase inhibitor for treatment of cyclic-AMP associated disorders

IN Macor, John E.; Carlson, Kenneth E.

PA Bristol-Myers Squibb Company, USA

SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002069905	A2	20020912	WO 2002-US6805	20020304 <--
	WO 2002069905	A3	20031009		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,				

	UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2439691	A1	20020912	CA 2002-2439691	20020304 <--
	AU 2002245601	A1	20020919	AU 2002-245601	20020304 <--
	US 2003069169	A1	20030410	US 2002-90258	20020304
	EP 1370211	A2	20031217	EP 2002-713772	20020304
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2005506286	T	20050303	JP 2002-569083	20020304
	HU 2006000103	A2	20060628	HU 2006-103	20020304
	US 2004229882	A1	20041118	US 2003-696761	20031029
	US 7067525	B2	20060627		
	US 2006025403	A1	20060202	US 2005-199464	20050808
PRAI	US 2001-273206P	P	20010302		
	US 2001-273291P	P	20010302		
	US 2001-289719P	P	20010509		
	US 2002-90288	A3	20020304		
	US 2002-90582	A3	20020304		
	WO 2002-US6805	W	20020304		

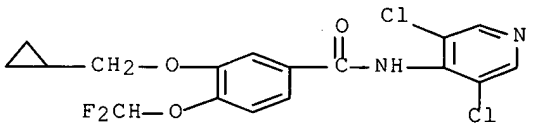
OS MARPAT 137:226646

AB Co-administration of a melanocortin receptor agonist, particularly an MC-1R or MC-4R agonist, and a cAMP phosphodiesterase inhibitor is described for modulating levels of cyclic adenosine 3',5' monophosphate (cAMP) in a mammal. The inventive co-administration is useful in the treatment of diseases affected by activity of cAMP-PDE, including without limitation, inflammatory bowel disease, irritable bowel syndrome, rheumatoid arthritis, osteoarthritis, pancreatitis, psoriasis, migraine, Alzheimer's Disease, Parkinson's disease, transplant rejection, asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, stroke, and neurodegeneration of, and consequences of traumatic brain injury.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Co-administration of melanocortin receptor agonist and cAMP phosphodiesterase inhibitor for treatment of cAMP-associated disorders)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 14 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:625535 CAPLUS Full-text

DN 138:180017

TI Experimental approaches for the treatment of the acute respiratory distress syndrome in a rat lung lavage model

AU Germann, Paul-Georg; Haefner, Dietrich

CS Department of Clinical Research, Byk Gulden Chemische Fabrik Lomberg, Konstanz, D-78467, Germany

SO Recent Research Developments in Respiratory & Critical Care Medicine (

2001), 1, 161-179
CODEN: RRDRBZ
PB Research Signpost
DT Journal; General Review
LA English

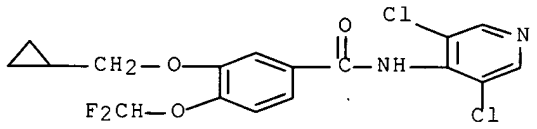
AB A review giving an overview and a closer insight into the histopathol. and pathophysiol. of the acute respiratory distress syndrome (ARDS). The different results of these exptl. investigations shown here were partly presented in more than 15 publications. Addnl. unpublished results are presented here for the first time. For this purpose, respiratory-physiol.-biochem. parameters (partial arterial oxygen pressure [PaO2], partial arterial carbon dioxide pressure [PaCO2]), immuno-& histol. (H&E, special stains, anti-rSP-C-antibody, substance distribution) and transmission-electron microscopic investigations in addition to the confocal-microscopic detection of fibrinogen in the lung were used as parameters. The first aim of these investigations is the characterization of histopathol. parameters of this exptl. model of ARDS-induction. This validation process should allow to assess the efficacy of different therapeutic approaches. The rat ARDS-lung-lavage model showed a good comparability of the histopathol. sequence in the early phase of the exudative state of the human ARDS, although in a shortened time period. The coded evaluation of the pulmonary edema formation, the influx of polymorphonuclear neutrophil leukocytes (PMNL) and especially the formation of hyaline membranes was shown to be an easy and comparable method to assess therapeutic effects. The anal. of the intrapulmonary distribution of the administered rSP-C-surfactant proved, that exogenously applied rSP-C-containing surfactant is homogeneously distributed in the lung parenchyma of an ARDS-lung. This could also be demonstrated with radioactive-labeled DPPC within the porcine ARDS-model. The administration of exogenous surfactant in an intact lung showed an nonphysiol., nonhomogenous distribution of the surfactant. The comparison of the different treatment time points showed, that the late treatment regimen (treatment 60 min after the ARDS-inducing lavage) is the more demanding ARDS-model due to its severe histopathol. changes. This model generates deeper insight into addnl. properties of the tested surfactant, such as the resistance against inactivation caused by plasma proteins. The results of our therapeutic approaches to treat ARDS showed the value of a surfactant-substitution therapy. This is evident because the treatment with surfactant led to inhibition of hyaline membrane formation and improvement of the arterial oxygen saturation The effects of the surfactant are significantly dose and substance dependent. Efficacy anal. between naturally derived and rSP-C surfactant, which is generated by recombinant DNA technol., showed that the rSP-C is equal or even superior in its therapeutic efficacy. The combination of rSP-C-surfactant and antiinflammatory therapies demonstrated that there are additive therapeutic effects of these combinations on the patho-histol. sequelae of the ARDS in this animal model. In particular the combination of rSP-C surfactant with steroids, an inhibitor of the complement factor C1, a phosphodiesterase-inhibitor of the type IV, and nonspecific cyclooxygenase inhibitor was tested. In the present work these pos. additive therapeutic effects could be demonstrated in a validated animal model for a phosphodiesterase-inhibitor of the type IV and the nonspecific (COX 1&2) cyclooxygenase inhibitor for the first time. The galenic combination of rSP-C surfactant together with a phosphodiesterase-inhibitor of the type IV exhibited the most impressive therapeutic effects. This combination of surfactant substitution and an addnl. antiinflammatory component is an useful therapeutic approach, because three different targets within the pathophysiol. of the ARDS can be reached: (1) respiratory function (alveolar epithelium & surfactant function), (2) alveolar-capillary leakage (endothelium and perivascular space), and (3) function of activated polymorphonuclear neutrophil leukocytes. A galenic-oriented development of surfactant combination therapy may reduce the amount of phospholipid burden in the lung. Furthermore, this development may use the

surfactant as a vehicle for addnl. therapeutic approaches. An effective galenic combination of a surfactant with addnl. therapeutic effects of antiinflammatory drugs will be the future direction in ARDS therapy. This recent data obtained from animal expts. will beneficially influence the clin. treatment of human ARDS.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase type IV inhibitor, in combined therapy with surfactant; exptl. approaches for the treatment of acute respiratory distress syndrome (ARDS) in a rat lung lavage model)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:575737 CAPLUS Full-text
DN 137:135500
TI Methods of inducing ovulation by administering a non-polypeptide cAMP level modulator
IN Palmer, Stephen; McKenna, Sean; Tepper, Mark; Eshkol, Aliza; MacNamee, Michael C.
PA Applied Research Systems Holding N.V., USA
SO U.S. Pat. Appl. Publ., 26 pp., Cont.-in-part of U.S. Ser. No. 928,268.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2002103106	A1	20020801	US 2001-14812	20011214	<--
	US 6953774	B2	20051011			
	US 2002065324	A1	20020530	US 2001-928268	20010810	<--
	CA 2469939	A1	20030626	CA 2001-2469939	20011214	
	AU 2002217111	A1	20030630	AU 2002-217111	20011214	
	AU 2002217111	B2	20070531			
	EP 1463493	A1	20041006	EP 2001-274987	20011214	
	EP 1463493	B1	20071003			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
	BR 2001017198	A	20041026	BR 2001-17198	20011214	
	CN 1582146	A	20050216	CN 2001-823951	20011214	
	JP 2005516924	T	20050609	JP 2003-552277	20011214	
	AT 374606	T	20071015	AT 2001-274987	20011214	
	MX 2004PA05782	A	20040913	MX 2004-PA5782	20040614	
	US 2005148501	A1	20050707	US 2005-498639	20050218	
	US 2006003925	A1	20060105	US 2005-169183	20050628	
	US 7078236	B2	20060718			
	US 2006293222	A1	20061228	US 2006-456033	20060706	

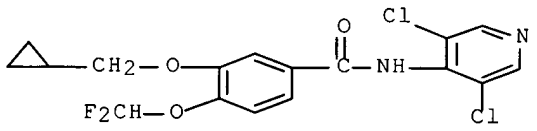
PRAI US 2000-224962P P 20000811
US 2001-928268 A2 20010810
US 2001-14812 A3 20011214
WO 2001-EP14730 W 20011214
US 2005-169183 A1 20050628

AB The present invention relates to methods of inducing ovulation in a female host comprising the administration of a non-polypeptide cAMP level modulator to the female host. In another aspect, the invention provides for specific administration of the phosphodiesterase inhibitor prior to the luteal phase of the host's ovulatory cycle. Preferred non-polypeptide cAMP level modulator include phosphodiesterase inhibitors, particularly inhibitors of phosphodiesterase 4 isoforms. Pharmaceutical compns. containing the cAMP modulators are also claimed.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of inducing ovulation by administering a non-polypeptide cAMP level modulator)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:462344 CAPLUS Full-text
DN 137:52364
TI New pharmaceutical preparation
IN Dietrich, Rango; Linder, Rudolf; Ney, Hartmut
PA BYK Gulden Lomberg Chemische Fabrik GmbH, Germany
SO Ger. Offen., 26 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

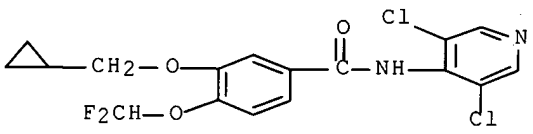
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10061137	A1	20020620	DE 2000-10061137	20001207 <--

PRAI DE 2000-10061137 20001207

AB The present invention concerns the area of pharmaceutical technol. and describes a new advantageous preparation for an active substance. The new preparation is suitable for the production of a multiplicity of pharmaceutical administrative forms. With the new preparation an active substance is present essentially evenly distributed in an excipient matrix from one or more excipients selected from a fatty alc., a triglyceride, a partial glyceride, and a fatty acid ester.

IT 162401-32-3, Roflumilast
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(new pharmaceutical prepns.)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:449485 CAPLUS Full-text
DN 137:24334
TI Pharmaceuticals comprising an active agent dispersed on a matrix
IN Dietrich, Rango; Linder, Rudolf; Ney, Hartmut
PA BYK Gulden Lomberg Chemische Fabrik G.m.b.H., Germany
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002045693	A1	20020613	WO 2001-EP14307	20011206 <--
	W: AE, AL, AU, BA, BG, BR, CA, CN, CO, CU, CZ, EC, EE, GE, HR, HU, ID, IL, IN, IS, JP, KR, LT, LV, MK, MX, NO, NZ, PH, PL, RO, SG, SI, SK, UA, US, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	CA 2430828	A1	20020613	CA 2001-2430828	20011206 <--
	AU 200216073	A	20020618	AU 2002-16073	20011206 <--
	EE 200300235	A	20030815	EE 2003-235	20011206
	EP 1341527	A1	20030910	EP 2001-999359	20011206
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001015987	A	20031223	BR 2001-15987	20011206
	JP 2004514736	T	20040520	JP 2002-547479	20011206
	HU 2004000566	A2	20040628	HU 2004-566	20011206
	CN 1523980	A	20040825	CN 2001-822381	20011206
	NZ 526015	A	20060331	NZ 2001-526015	20011206
	IN 2003MN00514	A	20050211	IN 2003-MN514	20030519
	NO 2003002593	A	20030805	NO 2003-2593	20030606
	MX 2003PA05092	A	20030905	MX 2003-PA5092	20030606
	ZA 2003005114	A	20040512	ZA 2003-5114	20030701
	US 2004058896	A1	20040325	US 2003-433398	20030911
	US 7175854	B2	20070213		
	US 2007122474	A1	20070531	US 2006-642621	20061221
PRAI	EP 2000-126847	A	20001207		
	WO 2001-EP14307	W	20011206		
	US 2003-433398	A1	20030911		

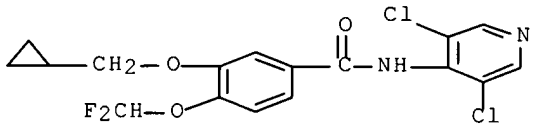
AB The present invention relates to the field of pharmaceutical technol. and describes a novel advantageous formulation for an active ingredient. The novel formulation is suitable for producing a large number of pharmaceutical dosage forms. In the new formulation, an active ingredient is present essentially uniformly dispersed in an excipient matrix composed of 1 or more

excipients selected from the group of fatty alc., triglyceride, partial glyceride and fatty acid ester. Cetyl alc. 50, glyceryl monostearate 5, cetyl palmitate 10, glyceryl tristearate 10 and paraffin 24.5 g are converted into a clear melt at about 90°. Roflumilast (0.5 g) is added, and the mixture is stirred until it is a clear solution The clear melt is prilled at about 70γC in a suitable vibration prilling unit.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical comprising active dispersed on matrix)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 18 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:354078 CAPLUS Full-text
DN 136:350569
TI Method of treatment of bronchial and respiratory disorders with a combination of a PDE4 inhibitor and a leukotriene antagonist
IN Chang, Yujun
PA USA
SO U.S. Pat. Appl. Publ., 3 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

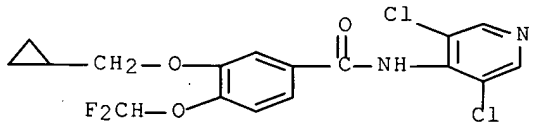
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002055520	A1	20020509	US 2001-3614	20011102 <--
	US 6528527	B2	20030304		
	CA 2427814	A1	20020516	CA 2001-2427814	20011102 <--
	WO 2002038155	A1	20020516	WO 2001-US45514	20011102 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002027123	A5	20020521	AU 2002-27123	20011102 <--
PRAI	US 2000-246368P	P	20001107		
	WO 2001-US45514	W	20011102		

AB Bronchial and respiratory disorders are treated by the sep., sequential, or simultaneous administration of (i) an amount of N-(3,5-dichloropyrid-4-yl)cyclopropylmethoxy-4-difluoromethoxybenzamide, the pyridyl N-oxide thereof, or a pharmaceutically acceptable salt of either compound; and (ii) an amount

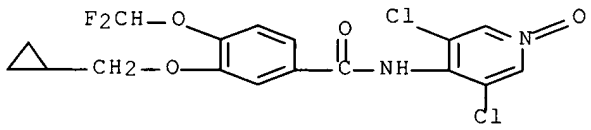
of a leukotriene antagonist, wherein the sum of the first and second amts. is a therapeutically effective amount

IT 162401-32-3, Roflumilast 292135-78-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of bronchial and respiratory disorders with a combination of a PDE4 inhibitor and a leukotriene antagonist)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 292135-78-5 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



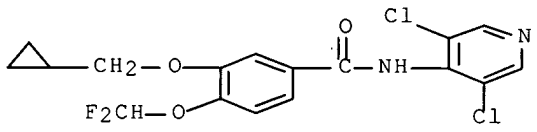
L8 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:340729 CAPLUS Full-text
DN 138:130747
TI Comparison of inhibition of ovalbumin-induced bronchoconstriction in guinea pigs and in vitro inhibition of tumor necrosis factor-α formation with phosphodiesterase 4 (PDE4)-selective inhibitors
AU Muise, Eric S.; Chute, Ian C.; Claveau, David; Masson, Paul; Boulet, Louise; Tkalec, Lydia; Pon, Douglas J.; Girard, Yves; Frenette, Richard; Mancini, Joseph A.
CS Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, Pointe-Claire-Dorval, QC, H9R 4P8, Can.
SO Biochemical Pharmacology (2002), 63(8), 1527-1535
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB PDE4 inhibitors elevate cAMP, and this elevation has been shown to inhibit inflammatory cytokines such as tumor necrosis factor-α (TNF-α). TNF-α was used as a biomarker to develop transcription-based assays to examine inhibition of PDE4 activity in human and guinea pig whole blood. In vitro inhibition by PDE4 inhibitors was measured by quant. PCR (qPCR) anal. of TNF-α mRNA in whole blood stimulated with lipopolysaccharide (LPS). The kinetics of human TNF-α mRNA production were highest 4 h following LPS stimulation. The guinea pig displayed kinetics of TNF-α transcription similar to those of humans. Anal. of inhibition of human TNF-α protein production was performed by immunoassay and shown to correlate with inhibition of transcription for

three of the four compds. tested (roflumilast, L-826,141, rolipram, and CT-2450). Roflumilast was 9-fold more potent for TNF-α inhibition in the qPCR assay than in the protein assay. The potencies of L-826,141 and roflumilast were determined in human and guinea pig whole blood by qPCR, with IC50 values of 270 and 20 nM, resp., in humans and 100 and 10 nM, resp., in guinea pigs. These results show that the potency of PDE4 inhibitors can be monitored in whole blood by a transcription-based assay, and that this type of assay can be adapted to various species provided the TNF-α nucleotide sequence is known. The in vitro whole blood IC50 for TNF-α inhibition was compared to inhibition in the ovalbumin-challenged guinea pig model of bronchoconstriction. The presence of plasma levels at the IC50 determined in vitro for L-826,141 and roflumilast provided significant inhibition of bronchoconstriction. This suggests that TNF-α can be used as a whole blood biomarker in the guinea pig for PDE4 inhibition in this inflammatory model.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); BIOL (Biological study)
(inhibition of bronchoconstriction and of tumor necrosis factor-α formation by phosphodiesterase 4-selective inhibitors such as)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:206426 CAPLUS Full-text

DN 136:335054

TI The new phosphodiesterase 4 inhibitor roflumilast is efficacious in exercise-induced asthma and leads to suppression of LPS-stimulated TNF-α ex vivo

AU Timmer, Wolfgang; Leclerc, Violette; Birraux, Guillaume; Neuhauser, Markus; Hatzelmann, Armin; Bethke, Thomas; Wurst, Wilhelm

CS Byk Gulden Pharmaceuticals, Konstanz, 78467, Germany

SO Journal of Clinical Pharmacology (2002), 42(3), 297-303
CODEN: JCPCBR; ISSN: 0091-2700

PB Sage Publications

DT Journal

LA English

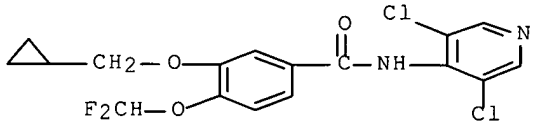
AB Roflumilast is a new phosphodiesterase 4 (PDE4) inhibitor developed by Byk Gulden Pharmaceuticals for the treatment of chronic obstructive pulmonary disease and asthma. A placebo-controlled, randomized, double-blind, two-period crossover study was performed to investigate the safety and efficacy of roflumilast in 16 patients with exercise-induced asthma. The patients received placebo or roflumilast (500 μg/day) for 28 days, each according to the randomly determined treatment sequences roflumilast/placebo and placebo/roflumilast. In both study periods, exercise challenge was performed 1 h after dosing on days 1, 14, and 28. FEV1 was measured before exercise challenge, immediately after the end of exercise challenge, and then at 1, 3, 5, 7, 9, and 12 min after the end of challenge. Blood samples for the determination of lipopolysaccharide (LPS)-stimulated tumor necrosis factor

alpha (TNF-α) in whole blood ex vivo as a surrogate marker for the inhibition of inflammatory cell activation were taken predose on days 1 and 28. Serial safety measurements were performed during both study periods. Anal. of variance for the crossover design showed a significant superiority of roflumilast over placebo on day 28. The mean percentage fall of FEV1 after exercise was reduced by 41% as compared to placebo ($p = 0.021$). An improvement of lung function during roflumilast treatment was also observed on days 1 and 14. The median TNF-α level decreased by 21% ($p = 0.009$) during roflumilast treatment but remained essentially constant under placebo. It is concluded that roflumilast is effective in the treatment of exercise-induced asthma. This result was accompanied by a significant reduction of TNF-α levels ex vivo. Treatment with roflumilast was safe and well tolerated.

IT 162401-32-3, Roflumilast
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of new phosphodiesterase 4 inhibitor roflumilast in exercise-induced asthma)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

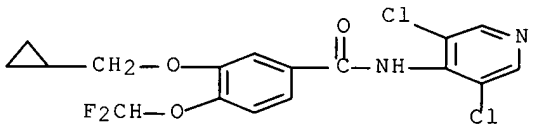
L8 ANSWER 21 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:183022 CAPLUS Full-text
DN 137:15735
TI Phosphodiesterase isoenzyme families in human osteoarthritis chondrocytes-functional importance of phosphodiesterase 4
AU Tenor, Hermann; Hedbom, Erik; Hauselmann, Hans-Jorg; Schudt, Christian; Hatzelmann, Armin
CS Department of Biochemistry, Byk Gulden Pharmaceuticals, Konstanz, D-78467, Germany
SO British Journal of Pharmacology (2002), 135(3), 609-618
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB We studied whether selective inhibitors of cyclic nucleotide hydrolyzing phosphodiesterase (PDE) isoenzymes influence IL-1β-induced nitric oxide (NO) release from human articular chondrocytes. In addition, the pattern of PDE isoenzymes contributing to cyclic nucleotide hydrolysis in human chondrocytes was characterized. Chondrocytes were isolated from human osteoarthritic cartilage and cultured in alginate beads. IL-1β-induced chondrocyte products (nitric oxide and prostaglandin E2) were measured in culture supernatants after 48 h incubation time. PDE activities were assessed in chondrocyte lysates. Inducible nitric oxide synthase (iNOS) and PDE4A-D proteins were detected by immunoblotting. The selective PDE4 inhibitors Piclamilast and Roflumilast partially attenuated IL-1β-induced NO production whereas selective inhibitors of PDE2 (EHNA), PDE3 (Motapizone) or PDE5 (Sildenafil) were inactive. Indomethacin reversed the reduction of IL-1β-induced NO by PDE4

inhibitors. It was shown that autocrine prostaglandin E2 (PGE2) enabled PDE4 inhibitors to reduce IL-1β-induced NO in this exptl. setting. Major PDE4 and PDE1 activities were identified in chondrocyte lysates whereas only minor activities of PDE2, 3 and 5 were found. IL-1β and cAMP-mimetics upregulated PDE4 activity and this was associated with an augmentation of PDE4B2 protein. Based on the view that nitric oxide contributes to cartilage degradation in osteoarthritis our study suggests that PDE4 inhibitors may have chondroprotective effects.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chondroprotective effect of phosphodiesterase inhibitors in human osteoarthritis and chondrocytes-functional importance of phosphodiesterase 4)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 22 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2002:174813 CAPLUS Full-text

DN 137:369935

TI Synthesis of [18F]labelled roflumilast using difluoro[18F]bromomethane as alkylating agent

AU Antoni, G.; Amschler, H.; Zech, K.; Langstrom, B.

CS Uppsala University PET Centre, Uppsala, S-751 85, Swed.

SO Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000 (2001), Meeting Date 2000, 375-376. Editor(s): Pleiss, Ulrich; Voges, Rolf. Publisher: John Wiley & Sons Ltd., Chichester, UK. CODEN: 69CIJC; ISBN: 0-471-49501-8

DT Conference

LA English

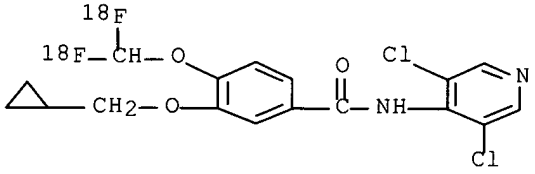
OS CASREACT 137:369935

AB The synthesis of [18F] labeled roflumilast was described using difluoro[18F]bromomethane as alkylating agent. Difluoro[18F]bromomethane was prepared from FCHBr2 and 18F in about 5% radiochem. yield and it was purified by preparative GC which removed fluorodibromomethane. [18F]Roflumilast was obtained together with [18F]F during the alkylation reaction. The low total radiochem. yield was due to the low recovery during the formulation of labeled Roflumilast as a suspension. However, this was enough for the PET investigations. For the oral administration, 15-25 MBq was used.

IT 475271-63-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of [18F]labeled roflumilast using difluoro[18F]bromomethane as alkylating agent)

RN 475271-63-7 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-[di(fluoro-18F)methoxy]- (9CI) (CA INDEX NAME)



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

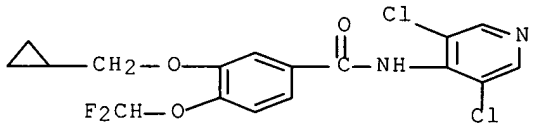
L8 ANSWER 23 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:127192 CAPLUS Full-text
DN 137:494
TI Lack of DNA binding in the rat nasal mucosa and other tissues of the nasal toxicants roflumilast, a phosphodiesterase 4 inhibitor, and a metabolite, 4-amino-3,5-dichloropyridine, in contrast to the nasal carcinogen 2,6-dimethylaniline
AU Jeffrey, Alan M.; Luo, Feng-Qi; Amin, Shantilal; Krzeminski, Jacek; Zech, Karl; Williams, Gary M.
CS Department of Pathology, New York Medical College, Valhalla, NY, 10595, USA
SO Drug and Chemical Toxicology (1977) (2002), 25(1), 93-107
CODEN: DCTODJ; ISSN: 0148-0545
PB Marcel Dekker, Inc.
DT Journal
LA English
AB The phosphodiesterase 4 inhibitor Roflumilast (B9302-107) (RF) and its metabolite 4-amino-3,5-dichloropyridine (ADCP) produced nasal toxicity in preclin. safety studies with rats. The purpose of this study was to assess the possible formation of DNA adducts, by RF and ADCP, in the nasal mucosa, liver and testes of male rats using the 32P-postlabeling assay. For comparison, rats were exposed to the DNA-reactive carcinogens 2,6-dimethylaniline (DMA), also known as 2,6-xylidine, a nasal carcinogen, and the aromatic amine carcinogens 4,4'-methylene-bis(2-chloroaniline) (MOCA), which yields monocyclic DNA adducts, and 2-acetylaminofluorene (2-AAF). In the case of RF, possible sources of DNA adducts include the parent mol. and its ADCP moiety by enzymic N-hydroxylation and sulfation, reactions typical of carcinogenic aromatic amines. 4-Acetoxylamino-3,5- dichloropyridine (N-acetoxy-ADCP), a chemical activated derivative of ADCP, was prepared and used to modify DNA which was then used to establish the chromatog. conditions with which to reliably detect whether or not such adducts were formed metabolically from RF and ADCP. Similarly, a standard N-hydroxy-DMA was prepared, but the corresponding N-acetoxy derivative was unstable and decomposed during synthesis. Both N-hydroxy-DMA and N-acetoxy-ADCP were mutagenic in the Salmonella typhimurium Ames assay using strain TA100 without an exogenous bioactivation system, with the former being more potent. N-hydroxy-ADCP was essentially inactive in this assay. For the 32P-postlabeling assay, male Wistar rats were exposed to the test substances and carrier control compds. by intragastric instillation at the selected dose levels for 7 days. Subsequently, the nasal mucosa, liver, and testes of the rats exposed to the test or control compds. were extirpated, the DNA extracted and the samples postlabeled. The patterns of adducts formed with the test compds. were compared to those formed in N-acetoxy-ADCP-and N-hydroxy-DMA-adducted DNA, which were assayed by both nuclease P1 and butanol enhancement methods. Based upon the similarity of results from the two enhancement methods, only the

former was used for the in vivo studies. No evidence was obtained for the formation of DNA adducts from RF or its metabolites, specifically ADCP, under the conditions of these assays despite the ability to detect adducts from DNA modified chemical with N-acetoxy-ADCP and DNA adducts from the other compds. in their target organs. In the absence of a pattern of compound-related spots, we conclude that RF does not form DNA adducts having the potential to initiate neoplasia in these three tissues.

IT 162401-32-3, Roflumilast
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA binding in nasal mucosa and other tissues of Roflumilast and its metabolite)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 24 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:916407 CAPLUS Full-text
DN 136:53755
TI Synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction
IN Garvey, David S.; Saenz de Tejada, Inigo; Earl, Richard A.; Khanapure, Subhash P.
PA Nitromed, Inc., USA
SO U.S., 117 pp., Cont.-in-part of U.S. 5,958,926.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6331543	B1	20011218	US 1999-387727	19990901 <--
	US 5874437	A	19990223	US 1996-740764	19961101 <--
	WO 9819672	A1	19980514	WO 1997-US19870	19971031 <--
	W: AU, CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 5958926	A	19990928	US 1998-145142	19980901 <--
	US 2002019405	A1	20020214	US 2001-941691	20010830 <--
	US 6462044	B2	20021008		
	US 2003023087	A1	20030130	US 2002-216886	20020813 <--
	US 6930113	B2	20050816		
	US 2004087591	A1	20040506	US 2003-694183	20031028
PRAI	US 1996-740764	A2	19961101		
	WO 1997-US19870	A2	19971031		
	US 1998-145142	A2	19980901		
	US 1999-387727	A1	19990901		
	US 2001-941691	A3	20010830		
	US 2002-216866	A3	20020813		

OS MARPAT 136:53755

GI

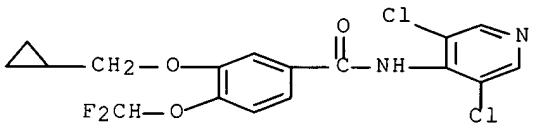
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. I-V, derivs. thereof, and certain substituted Ph and phthalzaine derivs. were claimed [D2 = H, alkyl, D; D = NO, NO2, alkyl, acyl, phosphoryl, silyl, etc.; A1-3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring; R8 = H, (halo)alkyl; p = 1-10; R24 = H, cyclohexyl, piperidinyl, etc., with the proviso that at least one of A1-3, J, or R24 contains T-Q or D; T = bond, O, S(O), amino; Q = NO, NO2; D1 = D or H; R37 = (hetero)aryl; R38 = H, halo, alkyl; G1 = alkyl, alkenyl or is part of a ring fused to the piperidine moiety of III; G4 = O, S; R40 = H, alkyl, haloalkyl, halo, etc.; R41 = alkyl, hydroxyalkyl, alkylcarboxy, etc.; R42 = aryl, alkylaryl, alkyloxyaryl; T1 = alkyl, oxyalkyl, thioalkyl, aminoalkyl]. Two synthetic examples were provided. E.g., the S-nitroso derivative of the 3-mercapto-3-methylbutyric acid ester of dipyridamole (VI) was prepared in 4 steps from dipyridamole in 3.5% overall yield. VI at doses of 10 and 30 μM was more efficacious in relaxing phenylephrine-induced tissue contraction than was the known phosphodiesterase inhibitor, dipyridamole. The present invention describes novel (nitrosated/nitrosylated) phosphodiesterase inhibitors, and compns. containing at least one (nitrosated/nitrosylated) phosphodiesterase inhibitor, and, optionally, one or more compds. that donate, transfer or release NO, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of NO, or is a substrate for nitric oxide synthase and/or one or more vasoactive agents. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing diseases induced by the increased metabolism of cGMP, such as hypertension, pulmonary hypertension, etc.

IT 162401-32-3D, Roflumilast, nitroso derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of nitrosated and nitrosylated (hetero)cyclic phosphodiesterase inhibitors used in treatment of sexual dysfunction)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 86 THERE ARE 86 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 25 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:868422 CAPLUS Full-text

DN 135:371647

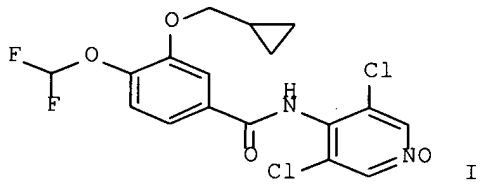
TI Fluoroalkoxy-substituted benzamide dichloropyridinyl N-oxide PDE4 inhibitor

IN Friesen, Richard; Ducharme, Yves; Girard, Yves; Li, Chun; Robichaud, Annette

PA Merck Frosst Canada & Co., Can.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001090076	A1	20011129	WO 2001-CA732	20010523 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2407780	A1	20011129	CA 2001-2407780	20010523 <--
	EP 1289961	A1	20030312	EP 2001-935872	20010523
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003534328	T	20031118	JP 2001-586265	20010523
	US 2002002191	A1	20020103	US 2001-864943	20010524 <--
	US 6448274	B2	20020910		
PRAI	US 2000-207023P	P	20000525		
	WO 2001-CA732	W	20010523		

GI

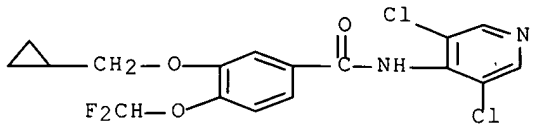


I

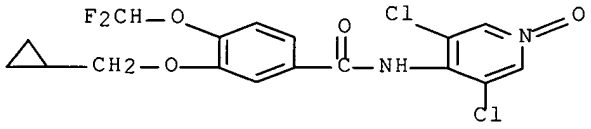
AB A PDE4 inhibiting compound (I) was prepared in 63% yield by refluxing 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide (II) with Mg monoperoxyphthalate hexahydrate in CH2Cl2/MeOH. The PDE4 inhibiting activity of I was determined in various tests, and it was shown that, although both I and II inhibit the enzyme, I does not significantly modify the duration of xylazine/ketamine anesthesia in rats whereas II causes a significant reduction, and that II readily crosses the brain barrier but I does not.

IT 162401-32-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidation of)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



IT 292135-78-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and PDE4-inhibiting activity of)
RN 292135-78-5 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 26 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:850920 CAPLUS Full-text
DN 135:366766
TI Method for enhancing cognitive function with phosphodiesterase-4 inhibitors
IN Hagan, James
PA Smithkline Beecham P.L.C., UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

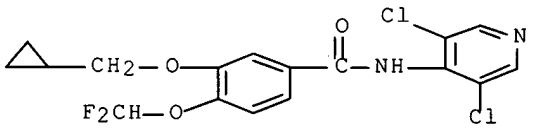
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001087281	A2	20011122	WO 2001-GB2134	20010515 <--
	WO 2001087281	A3	20020328		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1292287	A2	20030319	EP 2001-929824	20010515
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003533473	T	20031111	JP 2001-583749	20010515
	US 2003187006	A1	20031002	US 2003-275853	20030314
PRAI	GB 2000-11802	A	20000516		
	WO 2001-GB2134	W	20010515		

AB A method for enhancing cognitive function by administering to a patient in need thereof an effective amount of a PDE4 inhibitor.

IT 162401-32-3, Roflumilast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancing cognitive function with phosphodiesterase-4 inhibitors)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 27 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:810886 CAPLUS Full-text

DN 136:112393

TI The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis

AU Schmidt, Bernhard M. W.; Kusma, Matthias; Feuring, Martin; Timmer, Wolfgang E.; Neuhauser, Markus; Bethke, Thomas; Stuck, Boris A.; Hormann, Karl; Wehling, Martin

CS Institute of Clinical Pharmacology, Mannheim University Hospital, Ruprecht-Karls-University Heidelberg, Mannheim, D - 68167, Germany

SO Journal of Allergy and Clinical Immunology (2001), 108(4), 530-536
CODEN: JACIBY; ISSN: 0091-6749

PB Mosby, Inc.

DT Journal

LA English

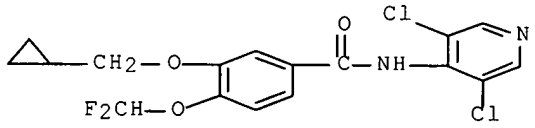
AB The beneficial effects of phosphodiesterase 4 (PDE4) inhibitors in allergic asthma have been shown in previous preclin. and clin. studies. Because allergic rhinitis and asthma share several epidemiol. and pathophysiol. factors, PDE4 inhibitors might also be effective in allergic rhinitis. The main objective of this study was to investigate the efficacy of oral roflumilast (500 μg/day) in allergic rhinitis. In a randomized, placebo-controlled, double-blinded, crossover study, 25 subjects (16 male, 9 female; median age, 28 yr) with histories of allergic rhinitis but asymptomatic at screening received roflumilast (500 μg once daily) and placebo for 9 days each with a washout period of at least 14 days in between treatment periods. In each of the treatment periods, controlled intranasal allergen provocation with pollen exts. was performed daily beginning the third day of treatment, each time approx. 2 h after study drug administration. Five and 30 min after each allergen provocation, rhinal airflow was measured by means of anterior rhinomanometry and the subjective symptoms obstruction, itching, and rhinorrhea were assessed by means of a standardized visual analog scale. Rhinal airflow improved almost consistently during the 9 days of roflumilast treatment, and it was significantly higher at study day 9 on roflumilast in comparison with placebo, a result also found for itching and rhinorrhea. With respect to the subjective obstruction score, a significant difference in comparison with placebo could be demonstrated within 4 days. This study shows that a PDE4 inhibitor, roflumilast, effectively controls symptoms of allergic rhinitis. Thus PDE4 inhibitors might be a future treatment option not only in

allergic asthma but also in allergic rhinitis or the combination of the 2 diseases.

IT 162401-32-3, Roflumilast
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase 4 inhibitor roflumilast is effective in treatment of allergic rhinitis)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:617813 CAPLUS Full-text

DN 135:170809

TI Pharmaceuticals for treating fibrotic diseases

IN Rennard, Steve I.; Kohyama, Tadashi

PA University of Nebraska Medical Center, USA

SO PCT Int. Appl., 12 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

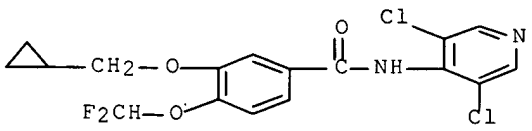
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001060358	A1	20010823	WO 2001-US4797	20010215 <--
	W: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1261331	A1	20021204	EP 2001-910707	20010215 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2004502643	T	20040129	JP 2001-559456	20010215
	US 2003018071	A1	20030123	US 2002-203583	20020809 <--
PRAI	US 2000-182876P	P	20000216		
	US 2000-227629P	P	20000824		
	WO 2001-US4797	W	20010215		

AB This invention relates to compns. and methods for preventing or treating fibrotic diseases by administering a phosphodiesterase 4-specific inhibitor. Thus, a controlled-release tablet contained Ariflo 3.3, dibasic Ca phosphate 88.5, Carbomer 934P 3.3, Carbomer 941P 1.6, Mg stearate 1.0, and Opadry White OY-S-9603 2.4%, and water qs.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceuticals for treating fibrotic diseases)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 29 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:338342 CAPLUS Full-text
DN 134:344605
TI Method for administering a phosphodiesterase 4 inhibitor
IN Murdoch, Robert D.; Torphy, Theodore J.; Zussman, Barry D.
PA Smithkline Beecham Corporation, USA; Smithkline Beecham P.L.C.
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001032165	A1	20010510	WO 2000-US29453	20001026 <--
	W: AE, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	ZA 2002003349	A	20030429	ZA 2002-3349	20000426
	CA 2389293	A1	20010510	CA 2000-2389293	20001026 <--
	BR 2000015039	A	20020625	BR 2000-15039	20001026 <--
	EP 1225884	A1	20020731	EP 2000-975385	20001026 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	TR 200201150	T2	20020923	TR 2002-1150	20001026 <--
	JP 2003513038	T	20030408	JP 2001-534370	20001026
	HU 2002003682	A2	20030428	HU 2002-3682	20001026
	NZ 518002	A	20040130	NZ 2000-518002	20001026
	AU 772909	B2	20040513	AU 2001-13445	20001026
	IN 2002MN00396	A	20070323	IN 2002-MN396	20020401
	BG 106623	A	20030228	BG 2002-106623	20020417 <--
	NO 2002001937	A	20020530	NO 2002-1937	20020424 <--
	MX 2002PA04220	A	20021017	MX 2002-PA4220	20020426 <--
	US 2003212112	A1	20031113	US 2003-429666	20030502
	IN 2005MN01344	A	20070615	IN 2005-MN1344	20051202
PRAI	US 1999-162477P	P	19991029		
	US 1999-162641P	P	19991101		
	US 2000-179817P	P	20000202		
	WO 2000-US29453	W	20001026		
	IN 2002-MN396	A3	20020401		
	US 2002-111957	B1	20020429		

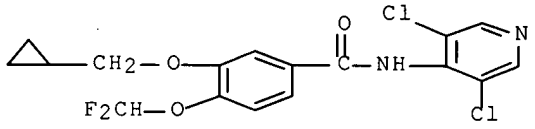
AB This invention relates to a method for increasing the dose of a PDE4 inhibitor that can be administered at one time and be tolerated by the patient by

reducing the absorption rate or the rate of rise in plasma concentration of the inhibitor. Immediated release tablets were prepared containing Ariflo.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administering a phosphodiesterase 4 inhibitor)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:240840 CAPLUS Full-text

DN 135:86928

TI In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor

AU Bundschuh, Daniela S.; Eltze, Manfrid; Barsig, Johannes; Wollin, Lutz; Hatzelmann, Armin; Beume, Rolf

CS Department of Pharmacology, Byk Gulden, Konstanz, Germany

SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(1), 280-290
CODEN: JPETAB; ISSN: 0022-3565

PB American Society for Pharmacology and Experimental Therapeutics

DT Journal

LA English

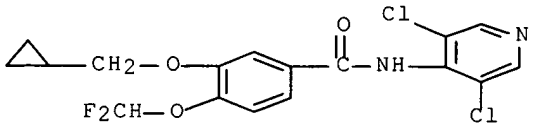
AB We have investigated the bronchodilator and anti-inflammatory properties of roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5- dichloropyrid-4-yl]-b enzamide), a novel, highly potent, and selective phosphodiesterase 4 (PDE4) inhibitor. Addnl., we compared the effects of roflumilast and its N-oxide, the primary metabolite in vivo, with those of the PDE4 inhibitors piclamilast, rolipram, and cilomilast. Roflumilast inhibited the ovalbumin-evoked contractions of tracheal chains prepared from sensitized guinea pigs (EC50 = 2+10-7 M) but showed no relaxant effect on tissues contracted spontaneously. In spasmogen-challenged rats and guinea pigs, i.v. administered roflumilast displayed bronchodilatory activity (ED50 = 4.4 and 7.1 μmol/kg, resp.). Furthermore, roflumilast dose dependently attenuated allergen-induced bronchoconstriction in guinea pigs (ED50 = 0.1 μmol/kg i.v.). Roflumilast given orally (ED50 = 1.5 μmol/kg) showed equal potency to its N-oxide (ED50 = 1.0 μmol/kg) but was superior to piclamilast (ED50 = 8.3 μmol/kg), rolipram (ED50 = 32.5 μmol/kg), and cilomilast (ED50 = 52.2 μmol/kg) in suppressing allergen-induced early airway reactions. To assess the anti-inflammatory potential of orally administered roflumilast, antigen-induced cell infiltration, total protein, and TNFα concentration in bronchoalveolar lavage fluid of Brown Norway rats were determined Roflumilast and its N-oxide equally inhibited eosinophilia (ED50 = 2.7 and 2.5 μmol/kg, resp.), whereas the reference inhibitors displayed lower potency (ED50 = 17-106 μmol/kg). Besides, orally administered roflumilast abrogated LPS-induced circulating TNFα in the rat (ED50 = 0.3 μmol/kg), an effect shared by its N-oxide, with both mols. exhibiting 8-, 25-, and 310-fold superiority to piclamilast,

rolipram, and cilomilast, resp. These results, coupled with the in vitro effects of roflumilast on inflammatory cells, suggest that roflumilast represents a potential new drug for the treatment of asthma and chronic obstructive pulmonary disease.

IT 162401-32-3, Roflumilast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

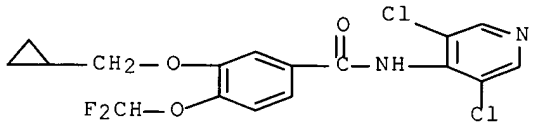
L8 ANSWER 31 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:240839 CAPLUS Full-text
DN 135:28819
TI Anti-inflammatory and immunomodulatory potential of the novel PDE4 inhibitor roflumilast in vitro
AU Hatzelmann, Armin; Schudt, Christian
CS Department of Biochemistry, Byk Gulden, Konstanz, Germany
SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(1), 267-279
CODEN: JPETAB; ISSN: 0022-3565.
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB From a series of benzamide derivs., roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5-di-chloropyrid-4-yl]b enzamide) was identified as a potent and selective PDE4 inhibitor. It inhibits PDE4 activity from human neutrophils with an IC50 of 0.8 nM without affecting PDE1 (bovine brain), PDE2 (rat heart), and PDE3 and PDE5 (human platelets) even at 10,000-fold higher concns. Roflumilast is almost equipotent to its major metabolite formed in vivo (roflumilast N-oxide) and piclamilast (RP 73401), however, more than 100-fold more potent than rolipram and Ariflo (cilomilast; SB 207499). The anti-inflammatory and immunomodulatory potential of roflumilast and the reference compds. was investigated in various human leukocytes using cell-specific responses: neutrophils [N-formyl-methyl- leucyl-phenylalanine (fMLP)-induced formation of LTB4 and reactive oxygen species (ROS)], eosinophils (fMLP- and C5a-induced ROS formation), monocytes, monocyte-derived macrophages, and dendritic cells (lipopolysaccharide-induced tumor necrosis factor-α synthesis), and CD4+ T cells (anti-CD3/anti-CD28 monoclonal antibody-stimulated proliferation, IL-2, IL-4, IL-5, and interferon-γ release). Independent of the cell type and the response investigated, the corresponding IC values (for half-maximum inhibition) of roflumilast were within a narrow range (2-21 nM), very similar to roflumilast N-oxide (3-40 nM) and piclamilast (2-13 nM). In contrast, cilomilast (40-3000 nM) and rolipram (10-600 nM) showed greater differences with the highest potency for neutrophils. Compared

with neutrophils and eosinophils, representing the terminal inflammatory effector cells, the relative potency of roflumilast and its N-oxide for monocytes, CD4+ T cells, and dendritic cells is substantially higher compared with cilomilast and rolipram, probably reflecting an improved immunomodulatory potential. The efficacy or roflumilast in vitro and in vivo (see accompanying article in this issue) suggests that roflumilast will be useful in the treatment of chronic inflammatory disorders such as asthma and chronic obstructive pulmonary disease.

IT 162401-32-3, Roflumilast
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(anti-inflammatory and immunomodulatory potential of roflumilast in vitro)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 32 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:196352 CAPLUS Full-text

DN 135:161992

TI Roflumilast: antiallergy/antiasthmatic, treatment of COPD, phosphodiesterase 4 inhibitor

AU Sorbera, L. A.; Leeson, P. A.; Castaner, J.

CS Prous Science, Barcelona, 08080, Spain

SO Drugs of the Future (2000), 25(12), 1261-1264
CODEN: DRFUD4; ISSN: 0377-8282

PB Prous Science

DT Journal; General Review

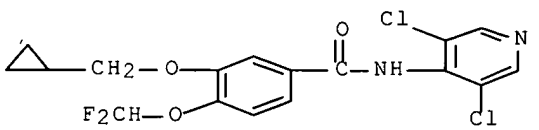
LA English

AB A review with 16 refs. regarding the drug roflumilast which is used to treat chronic obstructive pulmonary disease (COPD) and asthma. Topics discussed include its synthesis, description, pharmacol. actions, and clin. studies.

IT 162401-32-3, Roflumilast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiallergy/antiasthmatic roflumilast for COPD therapy)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:167792 CAPLUS Full-text
DN 134:227363
TI Topical use of kappa opioid agonists to treat otic pain
IN Gamache, Daniel A.; Yanni, John M.
PA Alcon Laboratories, Inc., USA
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001015678	A2	20010308	WO 2000-US22766	20000818 <--
WO 2001015678	A3	20020103		

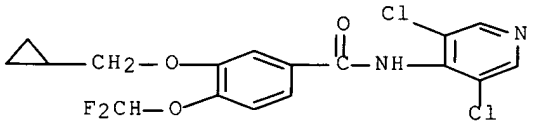
W: AU, BR, CA, CN, JP, MX, PL, TR, ZA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1999-387359 A 19990831

AB Topical or intranasal compns. and methods for treating otic pain caused by otitis, surgery, or swimmer's ear are disclosed. In particular, the invention discloses compns. and methods of using κ-opioid agonists locally for the prevention or alleviation of otic pain. Compns. also comprise antimicrobial, antiallergy, and anti-inflammatory agents to treat otic infections, allergies, and inflammations associated with otic pain. For example, an otic/nasal solution contained (by weight) a κ-opioid EMD-61753 0.01-1.0%, phosphate buffered saline 1.0%, Polysorbate 80 0.5%, and water up to 100%.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical compns. containing κ-opioid agonists for treatment of otic pain)

RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 34 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:167791 CAPLUS Full-text
DN 134:227362
TI Use of 5-HT1B/1D agonists to treat otic pain
IN Gamache, Daniel A.; Yanni, John M.; Sharif, Najam A.
PA Alcon Laboratories, Inc., USA
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001015677	A2	20010308	WO 2000-US22764	20000818 <--
	WO 2001015677	A3	20020328		

W: AU, BR, CA, CN, JP, MX, PL, TR, US, ZA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

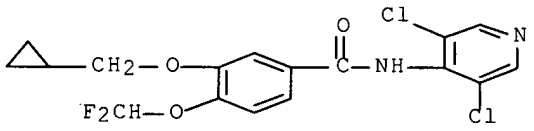
PRAI US 1999-387358 A 19990831

AB Topical otic or intranasal compns. and methods for treating otic pain caused by otitis, surgery, or swimmer's ear are disclosed. In particular, the invention discloses compns. and methods of using 5-HT1B/1D agonists for the prevention or alleviation of otic pain. Compns. also comprise an antimicrobial, antiallergy, and anti-inflammatory agent to treat otic infections, allergies, and inflammations associated with otic pain. For example, an otic/nasal solution contained CGS-12066A 0.01-1.0%, phosphate buffered saline 1.0%, Polysorbate 80 0.5%, and water up to 100% (weight/volume), resp.

IT 162401-32-3, Roflumilast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical compns. of 5-HT1B/1D agonists for treatment of otic pain)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 35 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN

AN 2001:152520 CAPLUS Full-text

DN 134:202703

TI Synergistic combination of a phosphodiesterase (PDE) inhibitor and a β2-adrenoceptor agonist for treatment of respiratory tract disorders

IN Beume, Rolf; Bundschuh, Daniela; Hatzelmann, Armin; Schudt, Christian; Weimar, Christian; Kilian, Ulrich

PA Byk Gulden Lomberg Chemische Fabrik G.m.b.H., Germany

SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001013953	A2	20010301	WO 2000-EP7852	20000811 <--
	WO 2001013953	A3	20010920		

W: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

	CA 2381802	A1	20010301	CA 2000-2381802	20000811 <--
	BR 2000013478	A	20020430	BR 2000-13478	20000811 <--
	EP 1212089	A2	20020612	EP 2000-954625	20000811 <--

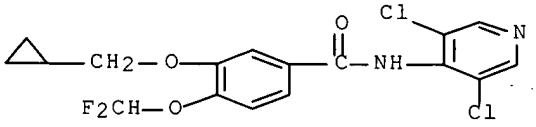
EP 1212089	B1	20060322			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
TR 200201317	T2	20021121	TR 2002-1317	20000811	<--
HU 2002003098	A2	20030128	HU 2002-3098	20000811	<--
JP 2003507435	T	20030225	JP 2001-518088	20000811	<--
NZ 517166	A	20040130	NZ 2000-517166	20000811	
AU 777012	B2	20040930	AU 2000-67016	20000811	
AT 320800	T	20060415	AT 2000-954625	20000811	
EP 1671651	A1	20060621	EP 2006-110822	20000811	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
PT 1212089	T	20060831	PT 2000-954625	20000811	
ES 2260043	T3	20061101	ES 2000-954625	20000811	
IN 2002MN00066	A	20050218	IN 2002-MN66	20020118	
NO 2002000815	A	20020219	NO 2002-815	20020219	<--
ZA 2002001389	A	20020821	ZA 2002-1389	20020219	<--
US 6624181	B1	20030923	US 2002-49999	20020220	
HR 2002000158	B1	20070831	HR 2002-158	20020220	
MX 2002PA01830	A	20020812	MX 2002-PA1830	20020221	<--
HK 1047244	A1	20061027	HK 2002-108936	20021209	
US 2004034087	A1	20040219	US 2003-437005	20030514	
US 7056936	B2	20060606			
US 2006079539	A1	20060413	US 2005-286391	20051125	
US 2006205806	A1	20060914	US 2006-433419	20060515	
PRAI EP 1999-116447	A	19990821			
DE 1997-19708049	A	19970228			
WO 1998-EP1047	W	19980224			
US 1999-367850	A2	19990827			
EP 2000-954625	A3	20000811			
WO 2000-EP7852	W	20000811			
US 2002-49999	A1	20020220			
US 2003-437005	A1	20030514			
US 2005-286391	A1	20051125			

AB The invention discloses the combined administration of PDE inhibitors and β2-adrenoceptor agonists for the treatment of respiratory tract disorders.

IT 162401-32-3, Roflumilast 292135-78-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase inhibitor-β2-adrenoceptor agonist synergistic combination for treatment of respiratory tract disorders)

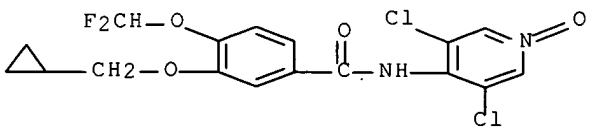
RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 292135-78-5 CAPLUS

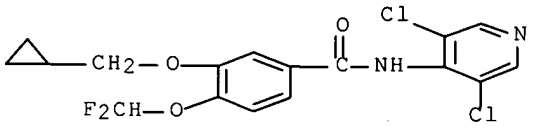
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



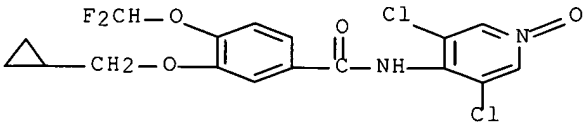
L8 ANSWER 36 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:790311 CAPLUS Full-text
DN 133:340267
TI Synergistic combination comprising roflumilast and a PDE-3 inhibitor
IN Amschler, Hermann; Beume, Rolf; Hafner, Dietrich; Schudt, Christian; Hatzelmann, Armin; Kilian, Ulrich
PA Byk Gulden Lomberg Chemische Fabrik Gmbh, Germany
SO PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000066123	A1	20001109	WO 2000-EP3838	20000427 <--
	W: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2372850	A1	20001109	CA 2000-2372850	20000427 <--
	EP 1176960	A1	20020206	EP 2000-927094	20000427 <--
	EP 1176960	B1	20040929		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002543133	T	20021217	JP 2000-615008	20000427 <--
	AT 277616	T	20041015	AT 2000-927094	20000427
	PT 1176960	T	20050228	PT 2000-927094	20000427
	ES 2228512	T3	20050416	ES 2000-927094	20000427
	US 6498173	B1	20021224	US 2001-959599	20011213 <--
	US 2003050329	A1	20030313	US 2002-286915	20021104
	US 6897229	B2	20050524		
PRAI	EP 1999-108808	A	19990504		
	WO 2000-EP3838	W	20000427		
	US 2001-959599	A3	20011213		

AB The invention relates to the combined use of the PDE4 inhibitor roflumilast, its salts or its N-oxide with a PDE3 inhibitor for the treatment of certain disease conditions such as acute or chronic obstructions of the bronchi. The dose in the case of PDE-3 inhibitor is typically in the range 0.1-25 mg/kg/day and the drugs can be administered as tablets, capsules, solns., etc.
IT 162401-32-3, Roflumilast 292135-78-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic pharmaceuticals comprising roflumilast and PDE-3 inhibitor)
RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 292135-78-5 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



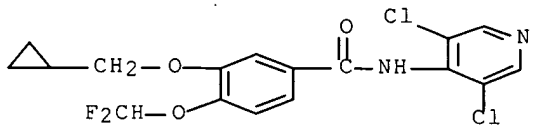
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:645852 CAPLUS Full-text
DN 133:217715
TI 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide, salts, and N-oxide for the treatment of multiple sclerosis
IN Amschler, Hermann; Hatzelmann, Armin; Schudt, Christian; Kley, Hans-Peter; Sanders, Karl
PA Byk Gulden Lomberg Chemische Fabrik G.m.b.H., Germany
SO PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

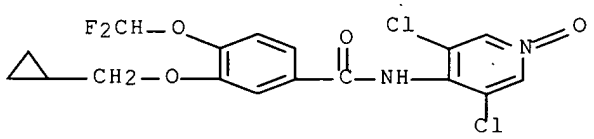
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000053182	A2	20000914	WO 2000-EP1703	20000301 <--
	WO 2000053182	A3	20010412		
	W: AE, AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2364258	A1	20000914	CA 2000-2364258	20000301 <--
	EP 1161239	A2	20011212	EP 2000-910736	20000301 <--
	EP 1161239	B1	20041020		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002538207	T	20021112	JP 2000-603671	20000301 <--
	AT 279924	T	20041115	AT 2000-910736	20000301
	PT 1161239	T	20050228	PT 2000-910736	20000301
	ES 2231162	T3	20050516	ES 2000-910736	20000301
	US 6531493	B1	20030311	US 2001-914763	20010905
PRAI	EP 1999-104793	A	19990310		
	WO 2000-EP1703	W	20000301		

AB 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4- yl)benzamide, a pharmacol. tolerable salt thereof or its N-oxide is used for the treatment of multiple sclerosis.

IT 162401-32-3 292135-78-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)benzamide, salts, and N-oxide for treatment of multiple sclerosis)
RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 292135-78-5 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



L8 ANSWER 38 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1998:568724 CAPLUS Full-text
DN 129:193729
TI Pharmaceutical compositions for the treatment of infant respiratory distress syndrome or adult respiratory distress syndrome containing 3-(cyclopropylmethoxy)-n-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide and a lung surfactant
IN Germann, Paul-Georg; Kilian, Ulrich; Beume, Rolf; Amschler, Hermann; Kruger, Uwe; Hafner, Dietrich; Eistetter, Klaus
PA Byk Gulden Lomberg Chemische Fabrik G.m.b.H., Germany
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9835683	A1	19980820	WO 1998-EP847	19980214 <--
	W: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19705924	A1	19980827	DE 1997-19705924	19970217 <--
	CA 2276429	A1	19980820	CA 1998-2276429	19980214 <--
	CA 2276429	C	20070619		
	AU 9864973	A	19980908	AU 1998-64973	19980214 <--
	AU 734122	B2	20010607		
	EP 977577	A1	20000209	EP 1998-910670	19980214 <--

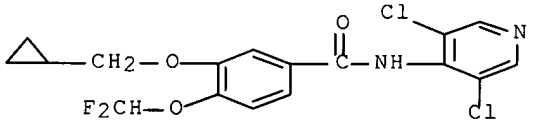
EP 977577	B1	20060816			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
EE 9900279	A	20000215	EE 1999-279	19980214	<--
EE 4094	B1	20030815			
BR 9807399	A	20000314	BR 1998-7399	19980214	<--
HU 2000001043	A2	20000928	HU 2000-1043	19980214	<--
HU 2000001043	A3	20021228			
NZ 336569	A	20010427	NZ 1998-336569	19980214	<--
JP 2001512452	T	20010821	JP 1998-535366	19980214	<--
CN 1123345	B	20031008	CN 1998-802597	19980214	
IL 130658	A	20040725	IL 1998-130658	19980214	
CZ 293871	B6	20040818	CZ 1999-2914	19980214	
PL 190775	B1	20060131	PL 1998-335134	19980214	
AT 336254	T	20060915	AT 1998-910670	19980214	
ES 2271990	T3	20070416	ES 1998-910670	19980214	
US 6436970	B1	20020820	US 1999-369455	19990806	<--
NO 9903875	A	19990811	NO 1999-3875	19990811	<--
NO 323594	B1	20070611			
HK 1026145	A1	20040702	HK 2000-105462	20000831	
US 2002132835	A1	20020919	US 2002-96258	20020313	<--
US 6998410	B2	20060214			
PRAI DE 1997-19705924	A	19970217			
EP 1997-102639	A	19970219			
WO 1998-EP847	W	19980214			
US 1999-369455	A3	19990806			

AB Novel compns. for the treatment of infant respiratory distress syndrome(IRDS) and adult respiratory distress syndrome (ARDS) are indicated which contain N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4- difluoromethoxy benzamide (I) and/or its pharmacol. tolerable salts and lung surfactant. A combination of 600 μg/kg I and 25 mg/kg lung surfactant improved the PaO2 values in rats as compared with the resp. lung surfactant alone. Thus, 8.2 g of 1,2-dipalmitoyl-3-sn- phosphatidylcholine, 3.46 g of 1-palmitoyl-2-oleoyl-3-sn-phosphatidylglycerolammonium, 2.7 g of I, 0.56 g of palmitic acid, 0.3 g of calcium chloride, and 0.2 g of r-SP-C (FF/I) were dissolved in 700 mL of 2-propanol/water (90:10) and spray-dried to obtain a fine, cream-colored powder.

IT 162401-32-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for treatment of infant respiratory distress syndrome or adult respiratory distress syndrome containing 3-(cyclopropylmethoxy)-n-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide and lung surfactant)

RN 162401-32-3 CAPLUS

CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)

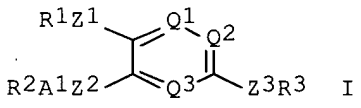


RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 39 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1997:218623 CAPLUS Full-text
DN 126:212048
TI Substituted aromatic compounds and their pharmaceutical use as inhibitors of TNF and PDE IV.
IN Aldous, David John; Smith, Graham Frank; Astles, Peter Charles; Pickett, Stephen Dennis; McLay, Iain McFarlane; Stuttle, Keith Alfred James; Ratcliffe, Andrew James; et al.
PA Rhone-Poulenc Rorer Limited, UK
SO PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9703967	A1	19970206	WO 1996-GB1746	19960722 <--
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
	AU 9665268	A	19970218	AU 1996-65268	19960722 <--
PRAI	GB 1995-15058	A	19950722		
	GB 1995-15729	A	19950801		
	GB 1996-4531	A	19960302		
	US 1996-14212P	P	19960327		
	WO 1996-GB1746	W	19960722		

OS MARPAT 126:212048
GI



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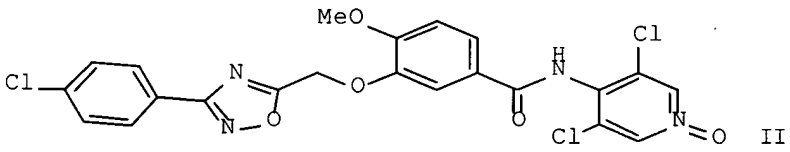


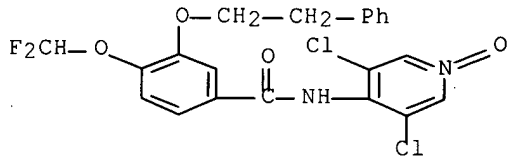
II

AB The invention describes compds. I [wherein R1 = (un)substituted alkyl, or when Z1 = bond, R1 may also = H; R2 = (un)substituted aryl, partially saturated bicycloaryl, heteroaryl, or RaRbN; R3 = (un)substituted aryl or heteroaryl; A1 = bond, (un)substituted C1-6 alkylene or C2-6 alk(en/yn)ylene optionally interrupted by O, S, phenylene, imino, alkylimino, SO, or SO2; Z1, Z2 = O, S or bond; Z3 = C.tplbond.C, CH2CZ, CZCH2, CZCZ, CH2NH, CH2O, CH2S, CH2SO, CH2SO2, CF2O, CZNH, NHCH2, OCH2, SCH2, SOCH2, SO2CH2, OCF2, OCZ, NHCZ, N:N, NHSO2, SO2NH, CZCZNH, NHCOO, OCONH, C(:NORc)CH2, C(F):N, CH(F)CH2, or NHCONH; Z = O or S; Ra, Rb = alkyl or arylalkyl; or NRaRb = 4- to 6-membered cyclic amine optionally containing addnl. O, S, NH, or NRc or substituted with oxo;

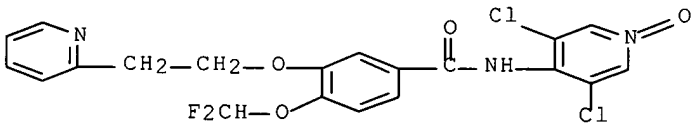
Rc = alkyl or arylalkyl; Q1, Q2, Q3 = CH, CX1, or N; and X1 = halo] and their N-oxides, prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates). The invention also describes processes for preparing I, pharmaceutical compns. comprising I, and their use in therapy as inhibitors of TNF and type IV cAMP phosphodiesterase (PDE) (no data). For example, 5-[[(3,5-dichloropyridin-4-yl)imino]fluoromethyl]-2-methoxyphenol (preparation given) was etherified with 3-(4-chlorophenyl)-5-(hydroxymethyl)-1,2,4-oxadiazole using the Mitsunobu reaction, followed by conversion of the imidoyl fluoride function to an amide using KOSiMe3, and N-oxidation using m-ClC6H4C(O)OOH, to give title compound II.

IT 187969-11-5P 187969-13-7P 187969-40-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted aromatic compds. as inhibitors of TNF and PDE IV)

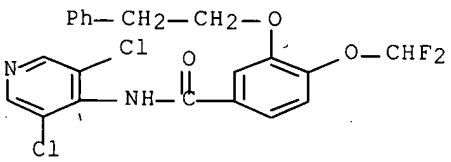
RN 187969-11-5 CAPLUS
CN Benzamide, N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)-3-(2-phenylethoxy)- (CA INDEX NAME)



RN 187969-13-7 CAPLUS
CN Benzamide, N-(3,5-dichloro-1-oxido-4-pyridinyl)-4-(difluoromethoxy)-3-[2-(2-pyridinyl)ethoxy]- (CA INDEX NAME)



RN 187969-40-0 CAPLUS
CN Benzamide, N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-3-(2-phenylethoxy)- (CA INDEX NAME)

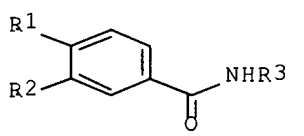


L8 ANSWER 40 OF 40 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:501321 CAPLUS Full-text
DN 122:239550
TI Preparation of fluoroalkoxy-substituted benzamides as cyclic nucleotide phosphodiesterase inhibitors.
IN Amschler, Hermann; Flockerzi, Dieter; Gutterer, Beate; Hatzelmann, Armin;

Schudt, Christian; Beume, Rolf; Kilian, Ulrich; Wolf, Horst P. O.
PA Byk Gulden Lomberg Chemische Fabrik GmbH, Germany
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9501338	A1	19950112	WO 1994-EP2169	19940702	<--
	W: AU, BG, BY, CA, CN, CZ, FI, HU, JP, KR, LV, NO, NZ, PL, RO, RU, SI, SK, UA, US					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	CA 2165192	A1	19950112	CA 1994-2165192	19940702	<--
	CA 2165192	C	20010424			
	AU 9474907	A	19950124	AU 1994-74907	19940702	<--
	AU 687087	B2	19980219			
	EP 706513	A1	19960417	EP 1994-924713	19940702	<--
	EP 706513	B1	20020515			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	CN 1126468	A	19960710	CN 1994-192659	19940702	<--
	CN 1046939	B	19991201			
	HU 73232	A2	19960729	HU 1995-3541	19940702	<--
	HU 220041	B	20011028			
	JP 08512041	T	19961217	JP 1994-503287	19940702	<--
	RU 2137754	C1	19990920	RU 1996-102569	19940702	<--
	PL 178314	B1	20000428	PL 1994-311820	19940702	<--
	CZ 290266	B6	20020612	CZ 1996-1	19940702	<--
	AT 217612	T	20020615	AT 1994-924713	19940702	<--
	PT 706513	T	20021031	PT 1994-924713	19940702	<--
	ES 2176252	T3	20021201	ES 1994-924713	19940702	<--
	SK 283263	B6	20030401	SK 1995-1617	19940702	
	US 5712298	A	19980127	US 1995-564322	19951219	<--
	NO 9505211	A	19951221	NO 1995-5211	19951221	<--
	NO 305598	B1	19990628			
	FI 9506333	A	19951229	FI 1995-6333	19951229	<--
	FI 112864	B1	20040130			
	HK 1011690	A1	20021011	HK 1998-112932	19981208	<--
	LV 13074	B	20040320	LV 2003-48	20030513	
PRAI	CH 1993-1996	A	19930702			
	WO 1994-EP2169	W	19940702			

OS MARPAT 122:239550
GI



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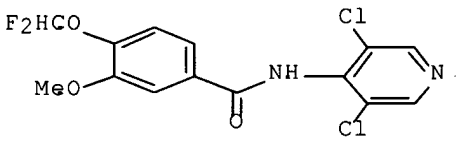


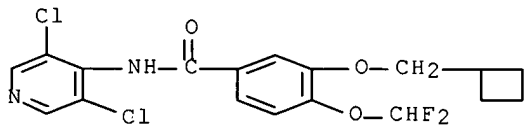
II

AB Title compds. [I; 1 of R1, R2 = H, alkoxy, cycloalkoxy, cycloalkylmethoxy, PhCH2O, totally or partially fluorinated alkoxy, and the other = totally or partially fluorinated alkoxy; R3 = (substituted) Ph, pyridyl], and N-oxides and salts thereof, were prepared Thus, 4-difluoromethoxy-3- methoxybenzoic acid (preparation given) was refluxed with SOCl2 in PhMe; the residue was

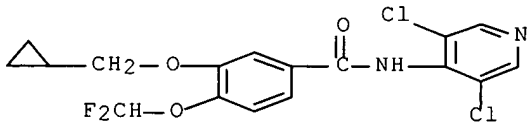
stirred with 4-amino-3,5-dichloropyridine and NaH in THF to give 58.6% title compound (II). I inhibited PDE type IV with -log IC50 = 8.42-9.18.

IT 162401-31-2P 162401-32-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of fluoroalkoxy-substituted benzamides as cyclic nucleotide phosphodiesterase inhibitors)

RN 162401-31-2 CAPLUS
CN Benzamide, 3-(cyclobutylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



RN 162401-32-3 CAPLUS
CN Benzamide, 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)- (CA INDEX NAME)



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2546449 PROCESS
L14 1 L8 AND PROCESS

=> dis l14 bib abs

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:625535 CAPLUS Full-text
DN 138:180017
TI Experimental approaches for the treatment of the acute respiratory distress syndrome in a rat lung lavage model
AU Germann, Paul-Georg; Haefner, Dietrich
CS Department of Clinical Research, Byk Gulden Chemische Fabrik Lomberg, Konstanz, D-78467, Germany
SO Recent Research Developments in Respiratory & Critical Care Medicine (2001), 1, 161-179
CODEN: RRDRBZ
PB Research Signpost
DT Journal; General Review
LA English
AB A review giving an overview and a closer insight into the histopathol. and pathophysiol. of the acute respiratory distress syndrome (ARDS). The different results of these exptl. investigations shown here were partly presented in more than 15 publications. Addnl. unpublished results are presented here for the first time. For this purpose, respiratory-physiol.-biochem. parameters (partial arterial oxygen pressure [PaO2], partial arterial carbon dioxide pressure [PaCO2]), immuno-& histol. (H&E, special stains, anti-rSP-C-antibody, substance distribution) and transmission-electron microscopic investigations in addition to the confocal-microscopic detection of fibrinogen

in the lung were used as parameters. The first aim of these investigations is the characterization of histopathol. parameters of this exptl. model of ARDS-induction. This validation process should allow to assess the efficacy of different therapeutic approaches. The rat ARDS-lung-lavage model showed a good comparability of the histopathol. sequence in the early phase of the exudative state of the human ARDS, although in a shortened time period. The coded evaluation of the pulmonary edema formation, the influx of polymorphonuclear neutrophil leukocytes (PMNL) and especially the formation of hyaline membranes was shown to be an easy and comparable method to assess therapeutic effects. The anal. of the intrapulmonary distribution of the administered rSP-C-surfactant proved, that exogenously applied rSP-C-containing surfactant is homogeneously distributed in the lung parenchyma of an ARDS-lung. This could also be demonstrated with radioactive-labeled DPPC within the porcine ARDS-model. The administration of exogenous surfactant in an intact lung showed an nonphysiol., nonhomogenous distribution of the surfactant. The comparison of the different treatment time points showed, that the late treatment regimen (treatment 60 min after the ARDS-inducing lavage) is the more demanding ARDS-model due to its severe histopathol. changes. This model generates deeper insight into addnl. properties of the tested surfactant, such as the resistance against inactivation caused by plasma proteins. The results of our therapeutic approaches to treat ARDS showed the value of a surfactant-substitution therapy. This is evident because the treatment with surfactant led to inhibition of hyaline membrane formation and improvement of the arterial oxygen saturation The effects of the surfactant are significantly dose and substance dependent. Efficacy anal. between naturally derived and rSP-C surfactant, which is generated by recombinant DNA technol., showed that the rSP-C is equal or even superior in its therapeutic efficacy. The combination of rSP-C-surfactant and antiinflammatory therapies demonstrated that there are additive therapeutic effects of these combinations on the patho-histol. sequelae of the ARDS in this animal model. In particular the combination of rSP-C surfactant with steroids, an inhibitor of the complement factor C1, a phosphodiesterase-inhibitor of the type IV, and nonspecific cyclooxygenase inhibitor was tested. In the present work these pos. additive therapeutic effects could be demonstrated in a validated animal model for a phosphodiesterase-inhibitor of the type IV and the nonspecific (COX 1&2) cyclooxygenase inhibitor for the first time. The galenic combination of rSP-C surfactant together with a phosphodiesterase-inhibitor of the type IV exhibited the most impressive therapeutic effects. This combination of surfactant substitution and an addnl. antiinflammatory component is an useful therapeutic approach, because three different targets within the pathophysiol. of the ARDS can be reached: (1) respiratory function (alveolar epithelium & surfactant function), (2) alveolar-capillary leakage (endothelium and perivascular space), and (3) function of activated polymorphonuclear neutrophil leukocytes. A galenic-oriented development of surfactant combination therapy may reduce the amount of phospholipid burden in the lung. Furthermore, this development may use the surfactant as a vehicle for addnl. therapeutic approaches. An effective galenic combination of a surfactant with addnl. therapeutic effects of antiinflammatory drugs will be the future direction in ARDS therapy. This recent data obtained from animal expts. will beneficially influence the clin. treatment of human ARDS.

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